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ON THE RELATIONS BETWEEN CORRESPONDING POINTS OF THE TWO RETINÆ.

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When the normal man looks at any object, say, a candle, in the ordinary way, he perceives only one candle, although two optical images are thrown upon his optic apparatus, one upon each retina, and each initiates a nervous process which, on being transmitted to the brain, is capable of producing a perception of the candle hardly distinguishable from that induced by the duplicate processes of binocular vision. This fact of "single vision," in spite of the duplication of the nervous processes necessary for vision in all the peripheral parts of the optic apparatus, has commonly been explained by the assumption (made by Newton, Johannes Müller, and Aubert, among other authorities) of a common cerebral centre for each pair of corresponding points; that is to say, it is supposed that the fibres of the optic nerves which carry to the brain the excitations initiated in any two corresponding points of the two retinæ are connected in the brain with one organ (cell, path, or centre) in which the sensations are excited, so that when the two corresponding points of the retinæ are simultaneously stimulated this central organ is thrown into a state of excitation which is the common psychical resultant of the two independent peripheral excitations.

Of recent years it has been pointed out by several authors that many facts of binocular vision cannot be reconciled with this hypothesis of a common cerebral centre for corresponding points; yet it would seem that it is still widely held. For, although the problem of the conditions of single vision (as it may, for brevity's sake, be designated) is not

touched upon by several of the most recent text-books on the senses, and though the doctrine of the common centre is repudiated or only vaguely and doubtfully suggested in others, this old assumption continues to appear in others; and it is necessarily implied by Hering's theory of the visual processes,[1] which still continues to find favour among a large number of physiologists and psychologists. It seems worth while, therefore, first to array the evidences which, as it seems to me, render this doctrine of a common centre wholly untenable: secondly, to indicate certain conclusions which must follow from its rejection: thirdly, to suggest a scheme of the anatomical and physiological relations of corresponding points which seems capable of accounting for most of the phenomena peculiar to binocular vision. The paper accordingly divides itself into three sections.

I.—*The Evidences of Separate Cerebral Paths for Corresponding Points.*

(1) Any illuminated surface appears no brighter (or but very slightly brighter) in binocular than in monocular vision; or, in other words, the simultaneously equal stimulation of corresponding points evokes a sensation of no greater (or of but very slightly greater) intensity than that evoked by similar stimulation of one of the points only.[2] Now, if corresponding points transmitted their excitations to a common centre, the excitement of that centre, and the resulting sensation, should be no less intense when two corresponding points simultaneously receive a stimulus of a given intensity than when one of them receives a physical stimulus of twice that intensity.

(2) Under certain conditions the stimulation of one of a pair of corresponding points not only adds nothing to the intensity of the sensation evoked by stimulation of its fellow, but actually diminishes it. This effect (generally known as Fechner's paradox) may most easily be observed by looking at any brightly illuminated surface with one eye only and, after a few seconds, opening the other eye behind a darkly smoked glass. At the moment of opening the second eye the surface seems to become very distinctly less bright. Yet, if the doctrine

[1] The logical necessity of this implication is sufficiently obvious, but will be exhibited on a later page.

[2] Observers are not in agreement on this point. It is generally said that in binocular vision the sensation is very slightly more intense; but Sherrington [14] could discover no such superiority. The comparison is a strangely difficult one, but my own observations lead me to the conclusion that dimly illuminated surfaces appear appreciably brighter in binocular than in monocular vision, but that with brightly illuminated surfaces no such difference is perceptible.

of a common centre were true, the feeble stimulation of the one area should add something, however little, to the intensity of the excitation of the common centre due to the stronger stimulation of the corresponding area.

(3) If an after-image is formed in one eye, and allowed to die away while the eyes remain at rest and shielded from all light, it may generally be revived several or many times by momentarily allowing a diffused and faint light to reach the stimulated retina through the closed eyelid. The admission of a similar diffused stimulus to the other eye may produce under favourable conditions a similar effect, but its influence is in this case very much feebler [3].

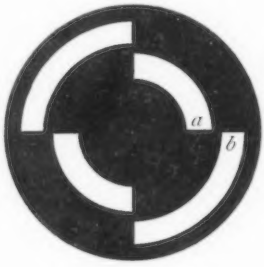

FIG. 1.

(4) On rapidly intermittent stimulation with light of given intensity, flicker-point (the rate of succession of stimuli which just suffices to extinguish flicker) is the same, or very nearly the same, whether the stimuli fall on one retina only (or simultaneously on both) or alternately on corresponding areas of the two retinæ (*i.e.*, are applied in such a way that, while the area of one retina is receiving the stimulus, its fellow receives no stimulus, but receives it in the succeeding moment, when the first is no longer under stimulation). Sherrington [14] has obtained this result by a very refined procedure, and I have confirmed it with a number of subjects by means of a very simple procedure. In a disc of mill-board windows are cut in the way indicated in fig. 1. The distance *a* to *b* is made equal to the interocular interval. The disc is set in rotation before an illuminated surface, and the subject looks at the surface through the disc, taking up a position such that one eye receives the rays from the surface through the outer pair of windows, the other through the inner pair. Flicker-point may then be conveniently determined by keeping the rate of rotation of the disc constant and varying

the illumination of the surface by moving the lamp nearer to, or further from, it. It is then found to be the same (or only very slightly different) whether both eyes are stimulated alternately or one is covered.

Now flicker, and the extinction of flicker, must be determined by processes in the cerebral centres (not improbably by the rate of succession of discharges of neurokyme across the synapses of the visual tract) [4]. If the corresponding points transmit their activities to a common centre, this centre must receive in a given time, when both eyes are stimulated at a given rate, but alternately, twice as many stimuli as when one eye alone is stimulated at the same rate. And if flicker is extinguished when the stimuli fall on one eye only at a given rate (say, thirty per second), then, when the two eyes are alternately stimulated, it should be extinguished by stimulation of each eye at half that rate (fifteen per second). But this, we see, is not the case; each eye requires to be stimulated thirty times per second.

(5) The following facts of binocular rivalry and fusion cannot be reconciled with the hypothesis of the common centre:—

(*a*) If two fields of slightly different texture and quality are combined binocularly, if, for example, one of them is marked by a slight flicker (Sherrington) [14], the observer is able to distinguish the peculiarities of the two fields by selective attention; and if the differences between them are made greater, one has no difficulty in directing the attention to the peculiarities of either field in turn. In the extremer instances of such differences (as when one uses a monocular microscope while keeping both eyes open) the one field may be wholly suppressed for consciousness; but every gradation between this total suppression of the one field and the full presence of both seems to be possible. (*b*) When two plain fields of different colour are projected upon corresponding areas of the two retinæ, one sees an alternation of the two colours with intervening periods of partial or complete fusion or blending of the effects of the two stimuli, which blending follows in the main the same rules as monocular colour mixture. This familiar fact of struggle or rivalry of the two colours is in itself difficult to reconcile with the hypothesis of a common centre; but a much greater difficulty is presented by the facts (*c*) that if the intrinsic muscles of one eye are paralysed with atropine during the experiment, an effort of accommodation causes the predominance of the colour presented to the unparalysed eye [5]; (*d*) that by a voluntary effort one can favour the predominance of either colour at will, even though the intrinsic muscles are paralysed [5].

(6) If one eye fixes for a few seconds or more a variegated field which moves constantly in one direction and is then directed upon a stationary surface, this appears for some little time to flow in the direction opposite to that of the former field. If, while one eye fixes the moving field, the direction of the motion is reversed every few seconds, and then after some minutes of such fixation the motion is maintained in one direction for a longer period, the illusory reversed motion is very much diminished in vividness and duration; it would seem that the physiological mechanism on which the illusory "after-image" of motion depends is fatigued by the prolonged stimulation of alternating direction. But the production of the after-image of motion in the other eye is not appreciably affected. This fact implies that the mechanism on which the "after-image of motion" depends exists in duplicate, one for each eye.[1]

(7) If "single vision" depended upon a conjunction of the central paths of corresponding points, we ought to find single vision strictly confined to corresponding points. But it is a well-known fact that disparate points may also subserve single vision so long as their disparation is small. Every stereoscopic combination involves such single vision with disparate points, and the stereoscopic effect is dependent upon it. Moreover, the degree of disparation compatible with single vision varies under practice and with slight changes of conditions, so that disparate images may be at one moment fused and at the next may fall apart and be seen as double images.

(8) It seems to have been fully established that in certain cases of squint, binocular vision involving fusion of widely disparate images exists, an abnormal system of correspondence having been acquired through use. And it seems to have been established also that in some of these cases, after the cure of the squint by surgical operation, the patient sees for some time double images, although the optical retinal images fall upon the normally corresponding points; and that these gradually give place to normal binocular vision, the normal system of correspondence becoming established by use and the abnormal system being broken up [1], [12]. This variability of the correspondence with practice is clearly difficult, if not impossible, to reconcile with the hypothesis of a common sensory centre for corresponding points.

(9) Perhaps the strongest evidence against the "common centre"

[1] These facts have been observed by Mr. A. Wohlgemuth, and are reported in a paper shortly to be published in the *British Journal of Psychology*. I have to thank Mr. Wohlgemuth for his permission to mention them here.

is afforded by the facts of functional blindness of one eye, whether occurring as a symptom of hysteria or induced by hypnotic suggestion. We seem compelled to believed that in such cases the sensory centre of the blind eye becomes functionally dissociated from the rest of the cerebrum or thrown into a state of paralysis (perhaps through a raising of its internal resistances), while that of the other eye continues to function normally; and both suppositions are incompatible with the hypothesis of a "common centre."

(10) The hypothesis of a "common centre" is supported by no evidence, except what slight presumption in its favour is afforded by the facts that the fibres carrying up impulses from corresponding points go to the occipital cortex of the same hemisphere, and that their centres or paths within that cortex lie so near together that when a lesion of this part of the cortex destroys the paths from one retina, the paths from the corresponding points of the other seldom escape injury. But it would seem that in some cases they do escape. Cases of hemianopia due to lesion of the occipital cortex on one side have been reported, in which, while the hemianopia was complete for one eye, small areas of the corresponding half of the other retina have retained their functions partially or completely [13]. It is clear that if these instances may be accepted as well established, they suffice to refute the doctrine of the "common centre."

(11) It seems that the owl, the frog, the chameleon, and other beasts of prey enjoy binocular vision in spite of the fact that in them the decussation of the fibres of the optic nerves at the chiasma is complete [14].

(12) Finally, the hypothesis of the "common centre" is founded upon a radical misconception of the conditions of fusion of effects of sensory stimuli. This misconception is that the sensation evoked by the stimulation of any sensory point or nerve-fibre comes into existence as an isolated or detached fragment of psychical existence, and that such fragments become compounded to form a consciousness only in so far as there obtains some special ground or cause of such compounding in the form of a corresponding fusion of the nervous conditions of the several sensations. To make this assumption is to invert the true statement, which may be formulated in the following way. In so far as sensory stimuli affect consciousness, they produce partial modifications of the complex but unitary whole of consciousness; and, when several stimuli simultaneously affect consciousness, their effects in consciousness can only be discriminated or distinguished from one another in so far as there obtains some special ground of distinction. Such special

grounds are of two principal classes—namely, differences of quality and differences of local signature of the several sensory effects or sensations, as we commonly call them; and the power of distinguishing or holding apart sensation-elements by aid of either of these grounds of distinction depends largely upon previous practice in active discrimination. The truth of these statements may be best brought home to us by reflection upon those sensory experiences in which the influence of local signature is at a minimum or absent. Thus we see clearly that in the province of auditory experience the discrimination of the sensation-elements that enter into a musical clang depends upon differences of their quality and upon previous practice and training in the discrimination of similar qualities. To the average untrained ear the tones of a clang are fused or confused in one whole; but the discrimination may be facilitated by differences of local signature. In a similar way odours and tastes blend or fuse with a degree of intimacy inversely proportional to their distinctness of quality.

When, therefore, we find sensations of similar quality fused in a manner that resists analysis (or, to speak more strictly, where stimuli, which evoke similar sensation-qualities when successively applied, are applied simultaneously, and conjointly produce a change in the sensory content of consciousness in which the effects of the two stimuli cannot be distinguished in any way from one another), we have not to seek any special physiological ground of this fusion of their effects to a common resultant, such as a fusion of the two sensory nerve-processes in some common centre; for such a fusion of effects in consciousness is the fundamental law of sensory processes. But, rather, when simultaneous stimuli evoke sensations of similar quality which nevertheless are distinguishable, then we have to seek some special ground for the possibility of this discrimination. It was by considerations such as these that Lotze was led to propound his celebrated doctrine of local signs.

If, now, we apply these considerations to the cases of the results of simultaneously stimulating pairs of corresponding and of disparate points, we see that the fact for the explanation of which some physiological ground must be sought is, not the fusion of effects of stimuli applied to corresponding points, but rather the fact that stimuli of similar quality applied to any other two points (whether of one retina or in the two retinæ respectively) produce effects in consciousness that are distinguishable. For corresponding points are points that have identical local signature; the spatial meanings attaching to their

sensational effects are identical, and therefore there is no ground for their distinction, no possibility of holding them apart in consciousness. And if we further ask, Why is their local signature identical? the best answer we can find seems to be—because the paths proceeding from any pair of corresponding points terminate in a common final path on the motor or efferent side; or, in other words, because the stimuli applied to any pair of corresponding points evoke the same motor tendency.

The facts and considerations stated in the foregoing pages seem to me to warrant the confident rejection of the hypothesis of a common sensory centre for corresponding retinal points and the assertion that the cerebral processes through which the stimuli applied to corresponding points produce their effects in consciousness take place in parts of the brain anatomically separate and distinct.

In another publication I propose to develop at length certain important implications of this conclusion [6], bearing upon the doctrine of psycho-physical parallelism, and here I wish only to insist upon its bearing upon the theories of the visual processes.

II.—*The Bearing of the Conclusion established in Section I on Theories of the Visual Processes.*

The conclusion is strongly favourable to the Young-Helmholtz theory, and wholly incompatible with Hering's theory of the visual processes. The most fundamental difference between the two theories is that expressed by the designation of the theories as those of the "component" and "opponent" processes respectively. The component theory, as usually understood and as formulated by Young and Helmholtz, implies that the composition of effects of visual stimuli exists only in the psychical sphere, only for consciousness; that, for example, when complementary rays stimulate the same part of one retina, or corresponding areas of the two retinæ respectively, the resulting achromatic sensation is the common effect or resultant in consciousness of three physico-chemical processes occurring in three separate and distinct groups of cerebral elements of specific constitution, which subserve the three primary qualities of visual sensation, red, green, and blue respectively.

Hering's theory of opponent processes, on the other hand, assumes that all the constituents of the mixed ray falling upon an area of one retina, or the two "complementary" rays falling upon corresponding

areas of the two retinæ and exciting achromatic sensation, act upon the same "visual substance" and produce in it a physico-chemical process which is the complex resultant of the several stimuli. Now the demonstration that "corresponding points" do not propagate their excitations to any common centre is at the same time a demonstration that no such complex physico-chemical resultant of the complementary stimuli as is assumed by the "opponent" theory can be formed when they fall upon corresponding areas; or, in other words, it follows that the effect in consciousness of stimulating corresponding areas with complementary rays (namely, achromatic sensation) is the common resultant of separate and distinct cerebral processes initiated in the two retinæ, and running their courses in anatomically distinct cerebral elements. And, if this is true in the case of achromatic sensation excited by complementary stimuli falling upon corresponding points, it is in the highest degree probable that it is true also of the achromatic sensation excited by complementary stimuli falling upon an area of one retina; for it can hardly be supposed that binocular colour mixture depends upon conditions radically different from those of monocular colour mixture.

If, then, the separateness of the cerebral paths or centres of corresponding points is established by the evidences reviewed above, it follows that the fundamental conceptions of Hering's theory of opponent visual processes are untenable.

These plain implications of the facts of binocular vision have been so completely overlooked, and my brief indication of them in a former publication [3] has been so completely ignored, that it seems worth while to present the argument in another and simpler fashion—namely, in relation to the problem of the nature of the yellow quality of sensation.

A necessary feature of the "opponent theory" is the view that yellow is a simple quality of sensation dependent upon (or correlated with) a cerebral process of one specific kind; whereas the "component theory" regards yellow as the psychical resultant of two simultaneously occurring cerebral processes which, when they occur successively, evoke sensations of red and green qualities respectively. And the alleged psychological simplicity of yellow (i.e., the impossibility of discovering in it unmistakable affinities to red and green, similar to the affinities to both red and blue that we discover in purple) is commonly claimed as one of the chief superiorities of the "opponent theory." Now, when corresponding areas are simultaneously stimulated with "red" and

"green" rays respectively, the effect in consciousness is (except during periods of rivalry or alternation of red and green) the yellow quality. But it has been proved that the corresponding points have no "common centre"; hence the yellow quality resulting from the binocular combination of red and green (or, more strictly, from the simultaneous stimulation of corresponding points with red and green rays respectively) is a psychical resultant of two separate cerebral processes, or, in the common phraseology, is a compound quality of sensation. Hence the proof of the separateness of the cerebral centres of corresponding points is fatal to Hering's theory of opponent visual processes, and is in harmony with, and strongly supports, the fundamental assumptions of, the component theory.

III.—*The Anatomical and Physiological Relations of Corresponding Points.*

It is, I think, possible to suggest a comparatively simple view of the anatomical and physiological relations of corresponding points which shall be in harmony with all the facts of binocular vision and will afford explanations of many of them.

I begin by accepting the essentials of Lotze's theory of local signature of the visual sensations as originally propounded by him—namely, the view that the local signature of the visual sensation excited by stimulation of any retinal point is bound up with, or is a function of, the motor tendency excited by stimulation of that point: and that all points of the retinæ stimulation of which evokes identical motor tendencies yield sensory effects of identical local signature. For my present purpose it is not necessary to enter into the obscure problem, How exactly does the motor tendency subserve local signature?

Now, corresponding points have identical motor tendencies, so far at least as concerns turning movements of the head and eyes (with the partial exception of movements of convergence of the eye-balls); and on this and other grounds we find good warrant for the assumption that the cerebral paths of any pair of corresponding points, although they remain separate throughout that part of them in which the qualities of sensation are determined, nevertheless converge in their distal or efferent parts upon a common motor path, the conjunction probably taking place in the subcortical region.

The identity of motor tendency thus secured to corresponding points is the ground of singleness of binocular vision, or, in stricter language, the absence of any sufficient difference of the motor tendencies

evoked by stimuli applied to two corresponding points renders the sensory effects of such stimuli spatially indistinguishable.

If now we add to this well-founded assumption that the paths of corresponding points issue in a common final path on the motor side, a second assumption, we have a sufficient anatomico-physiological scheme for the explanation of the facts of binocular vision. This second assumption is that the cerebral path from every point of either retina is connected either directly or indirectly with the path from every other point of the same retina in the manner that determines reciprocal inhibition, and that the paths of corresponding points are connected in the same way, that the relation of reciprocal inhibition obtains between them also. In my papers on the theory of the visual processes [3] I have shown how all the facts of light and colour contrast, as well as others, are adequately explained by the hypothesis that the relation of reciprocal inhibition obtains between all

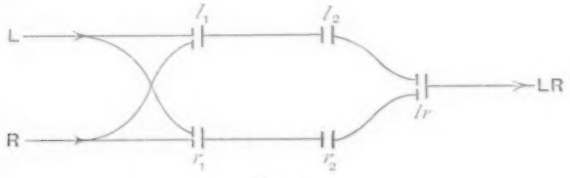

FIG. 2.

chains of retino-cerebral elements and is especially intimate between the members of each set of such elements subserving one of the primary qualities of visual sensation; and in my notes on smoothly graded contrast [7 and 8] I have described a peculiarly intense form of contrast which is well explained by the hypothesis of inhibition by drainage set out in another paper [9], but which presents great difficulties for any other theory of nervous inhibition. My present suggestion is, then, that the cerebral paths of corresponding points are connected together in their afferent parts in the way that all the paths from points of one retina are connected with one another—namely, in the way that renders possible reciprocal inhibition by drainage—as well as by convergence to a final common path at their efferent ends. This scheme seems to me to account for the facts more adequately than one briefly indicated in a note published some years ago [10].

The scheme may be represented diagrammatically in the simplest possible manner by fig. 2. In this diagram the paths right and left

from two corresponding points must be regarded as existing in triplicate at least in their middle or cortical parts; the three parallel chains of retino-cerebral elements of each triplicate path containing elements of three specific constitutions that subserve the three primary qualities of colour sensation, red, green, and blue respectively. And the relation of reciprocal inhibition, indicated in the diagram by the lines crossing over from R to L and from L to R, must be supposed to hold between all the chains of elements.

The middle parts of the lines L and R are meant to represent the cortical parts of the sensory paths; it is probable that their afferent parts are connected more directly with the final common path L R in the subcortical level as well as by the cortical paths, but it seems unnecessary and undesirable to complicate the diagram by introducing these lower-level paths.

Let me now briefly indicate how this scheme of the connexions enables us to account for some of the principal facts of binocular vision. With the exception of the facts of binocular perception of depth, of which I say nothing in this paper, the facts of binocular vision may be brought under the following three heads:—

(1) The fact of "single vision" with corresponding points—this is accounted for by the identity of their final common paths; for this means identity of motor tendency and therefore of local signature, or, in other words, it means lack of all ground for local discrimination of the sensory effects produced by stimulation of corresponding points.

(2) The reciprocal re-enforcement of processes initiated simultaneously at corresponding points—this is accounted for by the convergence to a final common path of the paths of corresponding points; for (naming the paths of the corresponding points R and L, and their final common path R L) the stream of impulses from the one path R, falling upon this final common path R L, will lower its resistances and so facilitate the discharge through it of the excitation of L.

(3) The facts of reciprocal inhibition—these are accounted for by the interconnexion of R and L in their afferent parts.

In the normal case of equal stimulation of corresponding areas with rays of similar composition, both paths R and L, in spite of their relation of reciprocal inhibition, function equally in virtue of their convergence to the final common path R L. In other cases of simultaneous and equal stimulation of paths in relation of reciprocal inhibition (as in the case of the reflex paths of antagonistic muscle groups) we commonly

observe an alternation of activity of the two paths. But we may suppose that in the case of the corresponding paths the reciprocal re-enforcement secured by the final common path R L prevents this alternation of activity of the paths R L and keeps both of them open throughout the period of stimulation.

In applying the scheme to explain Fechner's paradox, it is important to note that the paradoxical darkening of the field occurs only if the more intense stimulation of the one eye (say R) is applied to it some seconds before the less intense stimulus is applied to the corresponding area of the other eye, L, and that the darkening is more marked and of longer duration the longer this preliminary stimulation of R is continued. Under these conditions, two factors co-operate to enable the less stimulated path L to inhibit partially or completely the more intensely stimulated path R—namely, (*a*) fatigue of the path R, causing increase of its synaptic resistances at r_1 and r_2; (*b*) the open state of the final common path R L, or, in other words, the low resistance of synapse $l\ r$ due to the charged or active state of the path R L maintained by stimulation of R. It may be objected that $l\ r$, like r_1 and r_2, should have its resistance raised by fatigue: but this objection is, I think, met by the consideration that lower-level subcortical synapses such as $l\ r$ seem less subject to fatigue than the higher level or cortical synapses such as r_2 and l_2.

In binocular colour-rivalry the rivalry is more vivid and fusion is more difficult, the more pure and saturated are the two colours. These facts may be fully accounted for by introducing a small complication of the scheme—namely, by assuming that the corresponding chains of retino-cerebral elements subserving the same colour qualities converge at a higher level in the efferent part of the tract than those subserving sensations of different quality. For the higher the level of such convergence, the more would the activities of the two converging paths re-enforce or facilitate one another, and the more would their tendency to reciprocal re-enforcement, due to their efferent convergence, predominate over their tendency to reciprocal inhibition due to their afferent cross-connexions. Consider, then, the case of rivalry of red and green. When pure red and green rays fall on corresponding points, the tendency to reciprocal inhibition predominates, and vivid rivalry—*i.e.*, alternating activity of the two tracts—is the rule. But, when mixed rays are applied to corresponding points, in one of which the red, and in the other the green, component merely predominates a little over the others, the tendency to reciprocal re-enforcement predominates

over reciprocal inhibition, as in the case of rays of similar composition, and the rule is simultaneous activity of the paths from both retinæ and consequent fusion of the effects in consciousness of the processes initiated in both eyes, yielding a yellow of low saturation.

Closely allied with the last question is that of monocular colour fusion and rivalry. I have shown in previous publications that monocular rivalry of colours may constantly be observed under favourable conditions, of which the most important are intense stimulation and absence of re-enforcement by activity of the ocular muscles [3]. The question arises, if the paths of the one retina subserving two different colour-qualities, say red and green, are in the relation of reciprocal inhibition, as is implied by the phenomena of monocular colour-rivalry, why does fusion of their effects in consciousness occur so easily and generally, while, on similar stimulation of corresponding points, fusion is difficult, and rivalry or alternation the rule? I think the answer to this question must be that the paths of different colour-function arising from any one point of one retina have a strictly identical final common path, whereas corresponding points of the two retinæ have only partially identical final paths; for the final common path and the motor tendency of each retinal point must be conceived not as simple but as complex; and those of corresponding points must differ so far as convergent movements of the eyes are concerned, though they are identical in respect to all other ocular movements. And the completely identical final common path may be expected to secure more efficient reciprocal re-enforcement than is effected by one only partially identical.

All the phenomena classed together under the head of predominance of contours in the struggle of the two visual fields may be explained as due to the reciprocal re-enforcement of corresponding points. Consider, as a typical simple instance of predominance of contours, the case in which a large white ground fills the whole field of the right eye, while a white stripe on a black ground runs across the middle of the field of the left eye. In the binocular field the white stripe presented in the left eye appears upon the white field of the right eye, sharply bounded by dark lines which shade off into the full brightness of the field; that is to say, the white field of the right eye is inhibited along the borders of the combined field (see fig. 3).

Or consider the case in which the white field of the right eye is evenly bright, while the similar white field of the left eye contains black lines. The black lines appear as such in the binocular field—*i.e.*, the white field of the right eye is completely inhibited in those parts which correspond with the dark lines of the left field.

These and all other instances of predominance of contours may be generalized in the statement that the parts of the binocular field that are bright to both eyes predominate over and inhibit partially or completely the parts that are bright to one eye only. This general fact is fully accounted for by the scheme; the parts of the field bright to both eyes stimulate corresponding points whose cerebral paths re-enforce one another, while the parts of the field dark to one eye receive no such re-enforcement from the other eye, and are therefore inhibited by the re-enforced parts of the same field. Or to take as a concrete illustration the case described above of a white field to right eye and a white stripe on black ground to the left eye (fig. 3): the retino-cerebral paths of the right eye corresponding to those stimulated in the left eye by the white stripe are re-enforced by the activity of these corresponding paths of the left eye which play upon the same final common paths, and therefore they are enabled to inhibit completely the activity of the

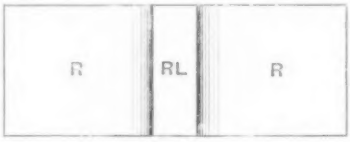

FIG. 3.

paths immediately adjoining them, and less completely those of remoter parts of the right retina; hence in the combined field the black borders of the white stripe shading off into full, or almost full, brightness of the rest of the monocular field.

This inhibitory effect of the combined field on the parts which are bright to the one eye only is instructively displayed if the white field of the right eye is combined with a white field of the left eye containing at its centre a black circle. If this circle is small the corresponding part of the right field is completely inhibited, and the circle appears fully black in the combined field. But if the black circle of the left field is made larger by successive steps, a point is soon reached at which only its peripheral part appears black in the combined field, while its central part appears a dull grey; and the larger the circle is made the brighter becomes this central part of the circle in the combined field. This is, of course, an illustration of the rule that border contrast is stronger than ground contrast, a rule which may be stated in terms of my inhibitory theory of contrast, as follows: the inhibitory tendency reciprocally exerted by any two cerebro-retinal paths is strongest between the paths of neighbouring retinal points, and is weaker in proportion to the remoteness of the two retinal points from one another.

Another case of binocular combination akin to the last is to my mind of peculiar interest, because it seems to afford strong evidence of the truth of the hypothesis of inhibition by drainage, as well as of the scheme of relations of corresponding points suggested above. If a full white field is presented to the right eye, and to the left eye a field consisting of a black ground with a small dull grey circle at its centre, Fechner's paradoxical effect is not obtained, but rather in the combined field the area of the circle appears brighter than any part of the monocular white field, and is surrounded by a dark zone in which the monocular field is inhibited.[1] In this case, then, the activity of the paths of the left retina stimulated by the grey circle re-enforces the corresponding paths of the right eye and enables them to inhibit the paths of the most closely adjoining points of the right retina. But the point of special interest is the excess of brightness of the combined field over all parts of the monocular field. If the circle of the left field be made of an intermediate brightness—*i.e.*, distinctly less bright than the field of the right eye, but still of fair brightness—this excess of brightness of the binocular part of the field over the monocular may be very considerable.

Now we have seen that when both fields are made equally and evenly bright, the binocular field is either no brighter than the monocular field, or its excess of brightness over the monocular field is very slight, opinions being divided on the question whether it is at all brighter than the monocular field. If we neglect this questionable (in any case very slight) excess of brightness of the binocular over the monocular field, we may say that the brightness of the binocular field is no greater than that of the brighter monocular component: or, in other words, there is no psychical summation of the intensities of the monocular fields. Yet in the special case we are now considering the brightness of the binocular part of the field appears greater than that of the monocular parts: although all parts of the right retina are equally stimulated, and the stimulus to the small area of the left eye is of less intensity. We are, I submit, compelled to believe that the excitation of the paths of the central part of the right retina corresponding to the stimulated part of the left retina is somehow intensified by the simultaneous feebler excitation of that part of the left retina; and this result is fully accounted for by the principles laid down above in the following way: The excitation of the central area of the left retina facilitates the excitation or passage of the current through the corresponding paths

[1] This statement does not hold true of every moment of the observation; for the binocular part of the field is apt to exhibit fluctuations of brightness.

of the right retina by playing upon their final common paths and so diminishing their resistance; this facilitation, however, would not in itself intensify the process in the cortical section of the corresponding paths of the right retina; but it enables these paths of the right retina to inhibit the equally stimulated paths of the surrounding parts of the same retina (as we see from the darkening of this surrounding area in the binocular field); and, since this inhibition is effected by drainage of neurokyme from those surrounding paths to the facilitated paths, the latter will transmit in each unit of time a larger quantity of neurokyme than they transmit under similar stimulation, but without facilitation from the corresponding paths of the left retina. The excess of neurokyme thus drained from the paths of surrounding areas and transmitted by the facilitated paths of the right retina is, then, the cause of the intensification of the brightness of the binocular part of the field. I can imagine no other way of explaining the phenomenon described, and I therefore regard it as affording strong support to the hypothesis of inhibition by drainage as well as to the scheme of connexions of corresponding points suggested in this paper.

One other phenomenon of binocular vision seems deserving of mention here. Sherrington [14] has shown that, if two equal and corresponding parts of the two retinæ are simultaneously stimulated, one by an intermittent stimulus, the other by a steady stimulus (or by one so rapidly intermittent as to be equivalent to a continued stimulus) of less, equal, or greater intensity, the flicker is damped, or, in other words, the flicker-point of the combined fields is lower than the flicker-point of the monocular field. I suggest that this damping of the flicker of the one field by continued stimulation of the corresponding area of the other retina may be the effect of the facilitation of the discharge of the "flickering" path, by the continued stimulation of the final path common to the corresponding areas. I do not pretend to attach much importance to this suggestion, in view of our ignorance of the cerebral conditions of flicker and its extinction; my suggestion is based on the view of these conditions indicated by any observations on the effects of a single momentary stimulation of the retinæ [4]. That view is that flicker depends upon the series of discharges across the cortical synapses induced by each momentary stimulus to the retina, and that extinction of flicker occurs when the retinal stimuli succeed one another so rapidly that a fresh cortical discharge and a fresh pulse of sensation are forced at so brief an interval that the intensity of its predecessor has not perceptibly declined. I showed in the paper referred to that the pulses

of sensation of lower intensity are of longer duration (flat-topped as it were); hence the flicker-point is lower in proportion as the intensity of the stimuli is lower. I suggest, then, that the facilitation or re-enforcement of the "flickering" paths by continued stimulation of the corresponding paths enables its cortical discharges to succeed one another more rapidly, or, without diminishing their intensity, gives them a longer duration or more "flat-topped" character. But these suggestions are so speculative that I will not attempt to work them out in detail. I merely throw them out for those readers who are interested in the problems of flicker.

Summary.

In the first section of this paper it is shown that the old doctrine of a "common cerebral centre" for corresponding points is wholly untenable, and that the paths of corresponding points are anatomically distinct in those central parts whose processes directly affect consciousness.

It was then shown that the secure establishment of this conclusion is necessarily fatal to Hering's theory of opponent visual processes.

A scheme of the relations of corresponding points was then suggested, according to which their paths are connected on the afferent side (like all the retino-cerebral paths of each retina) in the way which permits of reciprocal inhibition by drainage, and also at their efferent ends in a way which secures reciprocal re-enforcement. It was shown that many of the peculiar phenomena of binocular vision could be explained in terms of this scheme.

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THE PATHOLOGY OF PAPILLŒDEMA.

A Histological Study of Sixty Eyes.

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Introduction.

Our primary aim in the investigation on which the following paper is based has been to study the histological changes which the presence of an intracranial tumour may produce in the retina, disc and optic nerve. The principal type of change is that which has been known as optic neuritis, choked disc (Clifford Allbutt's translation of *Stauungspapille*), or papillœdema. We have sought to determine, as far as possible, the essential nature of this condition. During the past ten years it has fallen to the lot of one of us to examine ophthalmoscopically the eyes of nearly 700 cases of cerebral tumour in the wards of the National Hospital for the Paralysed and Epileptic, Queen Square, and in the present paper we attempt to interpret the various ophthalmoscopic features of papillœdema due to tumour of the brain, in terms of the histological changes we have found.

All the eyes examined were, with one exception, seen ophthalmoscopically by one or other of us during life; many were under observation for considerable periods before death, and full notes of the fundus changes were made from week to week. We have, in addition, examined several eyes from conditions where similar or allied changes in the disc or retina occur, and one section of our paper is devoted to their consideration. In the concluding portion we discuss the bearing of the histological changes which we describe on the arguments for and against the different hypotheses that have been advanced to explain the pathogenesis of papillœdema, and present the view that appears to us most in consonance with the facts.

The material used in the investigation has been, with the exception of one eye, obtained from cases in the National Hospital; and we are indebted to our colleagues on the staff of the Hospital for the facilities we have had in pursuing this work. We have examined in

all sixty eyes from thirty-nine cases. Fifty eyes were from cases with tumour papillœdema, and the other ten were from cases of meningitis, retrobulbar neuritis, pressure atrophy, albuminuric retinitis, and retinal vascular disease. We have had specimens from every stage of papill-œdema. In three cases we examined both eyes in the stage of commencing neuritis; in one of these the first signs had appeared only five days before death, and had reached a swelling of three dioptres the day before death; in another case the first change in the disc was seen within ten days of death. The majority of our patients died while the swelling was at its height. In three it had subsided into complete post-neuritic atrophy. In other cases, as a result of a decompressive cranial operation, the neuritis had subsided from different stages of its development; and finally, we had one case in which the neuritis had subsided after removal of the tumour, but had reappeared with its recurrence.

We have been fortunate in being able to remove many eyes a short time after death; in some of our most important cases they were obtained within two hours. This has enabled us to avoid the fallacies to which the examination of *post-mortem* eyes is apt to lead. The chief difficulty that meets any worker in this subject is, that the most important change, œdema, is liable to be influenced or modified, or, in the case of the nerve, even to be simulated, by the process of fixation. It has only been by the comparative examination of large numbers of sections both of normal and pathological specimens, that we have been able to form a definite opinion as to the presence or absence of certain pathological changes.

The majority of the discs were cut horizontally and parallel to the course of the entering vessels, but in five cases we cut them, along with the optic nerves, transversely in series, in order to determine the relative calibre of the vessels as they pass through the lamina cribrosa. The nerve, where possible, was examined in several different portions of its course—behind the bulb, in front of the exit of the vessels, through their exit, behind this point, in the optic foramen, and finally, in a few cases, the intracranial portion.

For the study of the general histology we used mainly hæmatoxylin, with Van Gieson's stain or eosin, but for the elucidation of certain points we employed the methods of Cajal, Bielschowsky, Marchi, Weigert-Pal, Donaggio, Unna-Pappenheim, and others. The Cajal and Bielschowsky methods were especially useful in investigating the nature of the changes in the nerve-fibres of the disc and retina.

Histology.

A. Œdema.—In specimens from any stage of papillœdema up to its full development, but before definite signs of atrophy or subsidence have appeared, simple œdema is the one predominant feature. This shows itself by a separation of the elements of the normal tissues, both parenchymatous and interstitial, by fluid which contains no cells and which has little tendency to coagulate. The origin of this fluid we must leave for later discussion. It is the presence of this œdema, unaccompanied in the great majority of cases by any sign of inflammation either acute or chronic, which is the one unfailing histological change found in tumour papillœdema. In many cases if the œdematous fluid could be by any process removed, the tissues would to all appearance be normal. Indeed in one case of very early œdema the shrinkage which necessarily results in the process of fixation was sufficient to bring the tissues back to a condition which it would be very difficult to describe as other than normal.

Fig. 1.

General view of papillœdema. Swelling + 5D. On the right (nasal) side of the disc the retina is merely displaced outwards; on the left it is raised and folded. Central vein congested; central pit bridged over by membrana limitans interna. Numerous small dilated vessels visible in section.

It is in the disc that the œdema produces most change. The fluid lying among the nerve-fibres and in the anterior layers of the lamina cribrosa separates and stretches these elements until they seem to form only a meshwork, in the interstices of which the fluid lies. The disc is thus increased in size in every diameter (fig. 1). The œdema appears first among the anterior layers of the lamina cribrosa, and the more peripheral bundles of nerve-fibres, and only later in the axial and intermediate bundles. As the disc swells lateralwards it displaces the retina, either raising it up from the pigment layer, or throwing it into a series

of folds which run concentric with the edge of the disc. This lateral bulging is in most cases due to the distension of the most peripheral

FIG. 2.

Section stained by Cajal's method to show course of nerve-fibres. On the right side the course is only slightly disturbed; on the left, the peripheral bundle of the nerve is compressed till it reaches the level of the membrane of Bruch; beyond this it is distended to form the main mass of the lateral bulge which raises the retina.

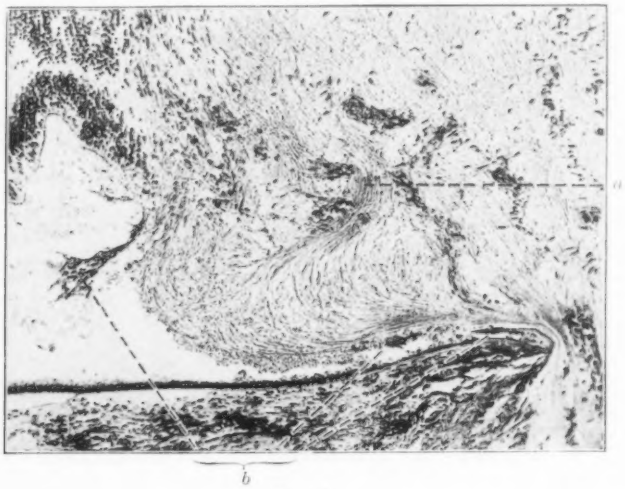

FIG. 3.

Part of fig. 1 under higher magnification. It shows the distortion of the course of the nerve-fibres which form the lateral bulge. At *a* some of the nerve-fibres are held back by vessels; *b* represents a ruptured membrane running from neighbourhood of *membrana limitans externa* towards the membrane of Bruch.

nerve-fibres alone, so that in section the whole bulge may be composed of a single nerve-bundle. The normal course of these fibres is conse-

quently very much disturbed; instead of curving gently forwards to the surface of the retina they turn outwards at an acute angle as soon as they pass the corner of the membrane of Bruch. Then they double on themselves, and finally curve upwards and outwards again to the surface, so that they take an S-shaped course (figs. 2 and 3).

In raising the retina away from the pigment layer this lateral bulging of the disc occasionally ruptures a fine cellular membrane which seems to run from the membrana limitans externa to the neighbourhood of the upturned end of the membrane of Bruch. This is probably the membrane which Verhoeff has described running from the membrana limitans externa to be reflected on to the surface of the membrane of Bruch; its cellular appearance is probably due to proliferative changes consequent on its stretching when it is ruptured. The displaced fibres are frequently also ruptured, and there is then generally a greater

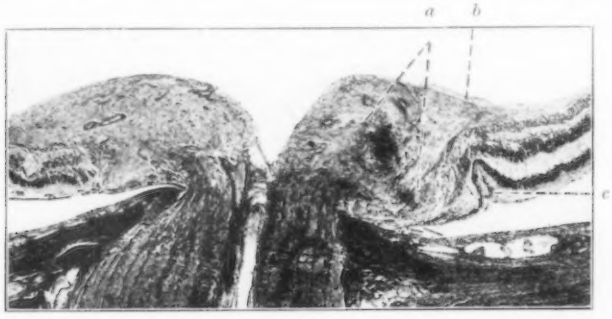

FIG. 4.

Intense papilloedema. Swelling + 7D. *a*, large area of degenerated and varicose nerve-fibres; *b*, raising of *membrana limitans interna*; *c*, folding of retina.

amount of subretinal exudate. Occasionally this membrane is stretched without rupturing, and under these circumstances, while the retina may be thrown into a number of folds its inner end is not raised from contact with the pigment layer.

As the swelling increases the axial bundles are lifted upwards and inwards so as to narrow the physiological pit, and the filling in of this is completed by the œdema which raises the inner limiting membrane from the central vessels.

The course of the intermediate nerve-bundles is very little modified, and their fibres as a rule are much less separated by œdema than those of the peripheral or axial bundles.

Occasionally it happens that the separation of the fibres of a bundle

is prevented in one part of its course by a band of the supporting tissue or by a vessel; when this happens to one of the peripheral bundles it adds a further complication to the distortion of its course (fig. 3). The greatest swelling and increase in the breadth of the disc as a whole takes place along a line drawn at right angles to the course of its fibres from the concavity of the first curve of the S to the upslope near the crest of the swelling; and, as will be seen, it is along this line, and more especially at either end, that the greatest changes, both degenerative and proliferative, are most prone to occur (fig. 4).

In some cases it happens, even when the swelling is at its highest point, that the physiological pit remains clear and the swelling of the temporal side of the disc is only very slight. As seen with the ophthalmoscope there may be a difference of six or seven dioptres between the level of the disc in this portion and the highest point of the swelling. Histological examination shows that this is due to the development of a specially dense band of connective tissue in the lamina cribrosa that runs from the neighbourhood of the central vessels towards the outer edge of the disc (fig. 5).

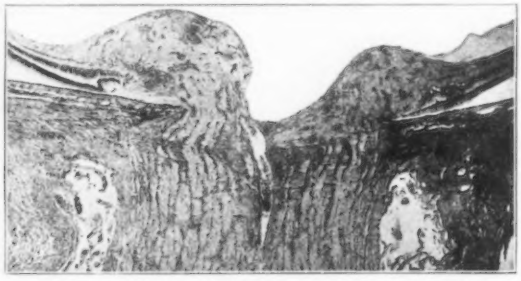

FIG. 5.
Papilloedema. Swelling + 4·5 on nasal side of disc, the central pit remaining clear.

So far we have dealt mainly with the effects of the œdema on the nerve-fibres of the disc; the changes produced in the supporting tissues are just as profound. The posterior dense layers of the lamina cribrosa are unaltered in position, and their fibres little if at all separated in the great majority of cases. They run as a compact band straight across, or with a slight convexity backwards; in one case, however, even the posterior fibres were separated a little by œdema, and had become convex forwards. On the other hand, the anterior layers become more separated the further forwards we go, so that the most anterior fibres,

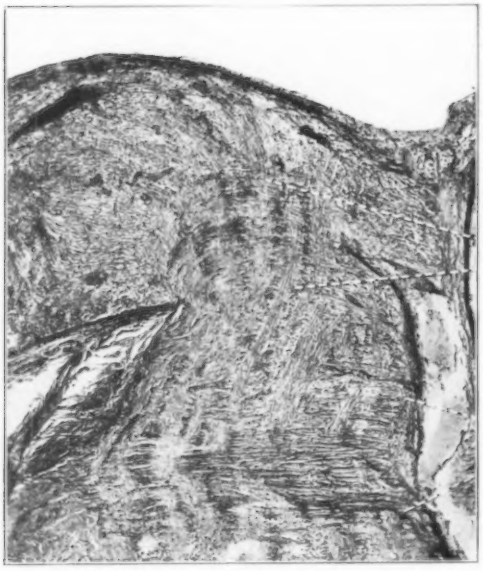

FIG. 6.

Papillœdema ten days after commencement. *a*, main mass of lamina cribrosa, normal in position; *b*, anterior fibres curved forward and separated from one another.

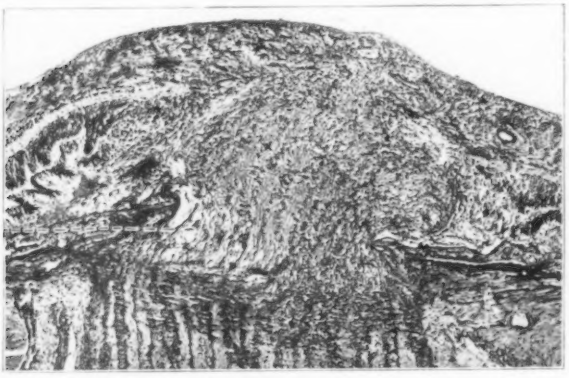

FIG. 7.

Papillœdema. Swelling + 7D, lamina cribrosa slightly convex backwards. *a*, œdema separating nerve-fibres down to level of lamina cribrosa.

corresponding to the pars choroidalis, are carried out into the crest of the swelling, and so stretched and attenuated as to be barely recognizable (fig. 6). Occasionally the œdema extends behind the level of the scleral angle down to the compact portion of the lamina, and separates the nerve-fibres here from one another; but owing to the resistance that the ring formed by the membrane of Bruch offers the fibres become again compact as they pass through it (fig. 7).

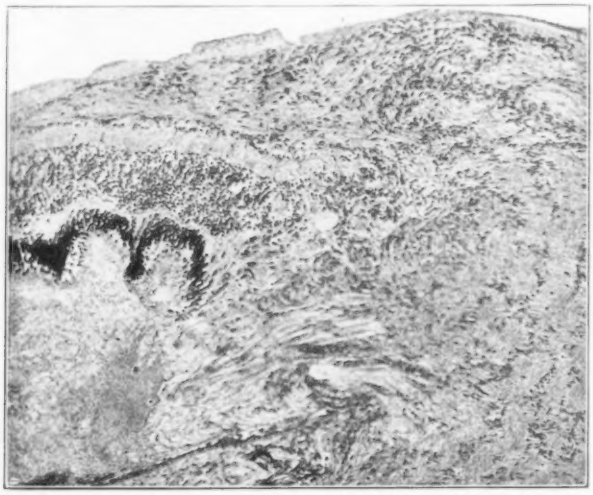

FIG. 8.

To show the rupture of fibres in the lateral bulge; folding of the retina; a few scattered cytoids; and raising of membrana limitans interna.

The separation of the fibres of the nerve-fibre layer by œdema can be traced out for a short distance in all directions. In the majority of cases the œdema remains among the nerve-fibres, but in a few of the more severe cases the membrana limitans interna is raised into small vesicles, which contain exudate, and are traversed by the stretched or ruptured fibres of Müller. These vesicles are most frequently seen towards the outer edge of the swelling on the macular side (figs. 4 and 8). They give rise to the appearance seen in cases of intense papillœdema of a fan-shaped figure of bright white dots with the apex of the fan pointing towards the macula. It is over the part of the retina in which the fibres constituting the papillo-macular bundle run that this fan lies, and it is probably because these have a short course, and consequently

a limited distensibility, that the exudate makes more room for itself by raising up the membrana limitans interna.

Our observations thus bear out fully Marcus Gunn's hypothesis [21] as to the formation of the macular fan; it is produced by excess of fluid in the nerve-fibre layer which is forced into a fan formation by the anatomical arrangement of the nerve-fibres in the area affected. In an earlier paper by one of us [50] some clinical arguments in favour of this view were brought forward. The presence of a well-marked macular fan is not inconsistent with the retention of perfectly good vision; this argues strongly against it being due to degenerative changes. In cases which recover, the macular fan may disappear without leaving a trace behind, which is comprehensible if, as we believe, it is due simply to beads of œdematous fluid raising up the membrana limitans interna.

Apart from the folding and displacement the œdema produces comparatively little change in the other layers of the retina; even when they are affected it is only in the immediate neighbourhood of the disc. The elements of the inner nuclear layer may be separated so that under low magnification this appears to be made up of two layers divided by a clear space, but more usually there is only a little irregular spacing in its folded part. The outer molecular layer is often œdematous beyond the folds, but it never contains the large cavities filled with coagula that are so characteristic of albuminuric retinitis. The outer nuclear layer is rarely, if ever, affected.

A serous exudate free from cells generally lies in the folds of the retina, but the fact that we have had only *post-mortem* material available introduces a difficulty in dealing with this question of the subretinal exudate. Some of the eyes we examined were not removed till several hours after death, and the disintegration of the rods and cones had sometimes reached a fairly advanced stage, but when we managed to obtain an early autopsy these were generally well preserved. Unlike the œdema elsewhere this subretinal exudate tended to coagulate, but this may be simply the result of the presence of products of *post-mortem* disintegration or of subretinal extravasations.

To summarize: The mechanical effects of œdema within the bulb are restricted to the disc and its immediate neighbourhood, and the retina is affected only by the swelling of the disc and the spread of fluid from it.

It is more difficult to determine the presence or assert the absence of œdema in the extra-bulbar portion of the nerve. The comparatively

unyielding pial sheath and the partition of the nerve by strong connective tissue septa passing from the pia must prevent any great separation of the nerve-fascicles such as occurs in the disc. It is necessary, moreover, to exercise great care in discriminating between appearances that may be due to *post-mortem* shrinkage or to fixation, and those produced by *ante-mortem* pathological processes, and it has only been by the examination and comparison of a very large number of sections that we have been able to arrive at any definite conclusion as to the distribution of œdema in the nerve.

There is frequently a definite difference between the appearance of the vessel-bearing portion of the nerve and of that part of it behind the entrance of the central vessels; indeed, this marked difference is a strong argument in favour of the pathological nature of the change found in the anterior portion. Here in some cases in which the

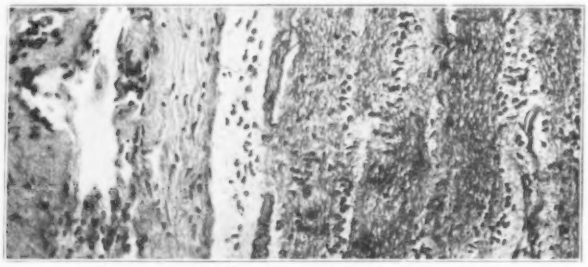

FIG. 9.

Longitudinal section of the optic nerve near the eye. *a*, nerve-fibre bundles; *b*, œdema in subpial zone (*Gliamantel*); *c*, *pia mater*; *d*, subarachnoid space.

papillœdema is considerable there is a layer of œdema immediately under the pia. It appears as a pale band made up of a meshwork of fine trabeculæ containing a few glial nuclei. It is, in fact, the normal peripheral zone of neuroglia (Fuch's *Gliamantel*) that is infiltrated by the œdema (fig. 9). This band varies in size, sometimes being as broad as a normal nerve-fibre bundle. The œdema is usually not present in the whole circumference of the nerve, or if so it may be more marked at one part than at another. There is occasionally œdema along the septa and round the axial strand containing the central vessels, but it is not as a rule so definite as in the subpial zone.

The œdema of the nerve diminishes rapidly at the entrance of the central vessels and usually disappears a little behind this point. We

were never able to detect any œdema in the intracranial portion of the nerve.

B. The vascular changes.—The vascular changes in papillœdema consist mainly in venous and capillary congestion. The arteries, at least in the pre-atrophic stages, seem to be unaffected. The effects of this venous and capillary congestion are, like the œdema, most obvious in the disc itself and in its immediate neighbourhood. The larger veins in the disc are dilated, usually full of blood, which often contains an excess of polymorphonuclear leucocytes. In the zone of the swollen disc which corresponds to the anterior layers of the lamina cribrosa there are numerous small dilated venules and capillaries, most numerous at a point just inside the lateral bulging of the nerve-fibres. Evidences of capillary and venous congestion may be also seen in the retina, especially in the nerve-fibre layer, for a short distance from the disc margin. Beyond the radius of the macular region there is usually little obvious change. The central vein in its passage through the denser part of the lamina cribrosa shows no dilatation; its lumen is smaller than in the looser tissues in front, but this seeming diminution is only relative, and is due to the fact that the more unyielding tissue of the lamina prevent its dilatation. In the looser tissues behind the lamina it again dilates and as a rule remains dilated in the whole of its intraneural course. It passes from the centre of the nerve towards the pia usually before the artery and often winds round the nerve under the pial sheath. In this part of its course its lumen is still generally well open, but after it has passed through the pia and is lying in the subarachnoid space its walls are collapsed and its lumen is simply a slit (figs. 10 and 11). Traced in serial sections it is found to remain in this condition in its passage through the subdural space and in the dura mater until it reaches the looser tissues in the outer part of the sheath. The numerous smaller veins and the capillaries in the pial sheath and in the septa are also in a condition of congestion.

A further evidence of vascular congestion is afforded by the hæmorrhages which may occur everywhere on the disc and in the retina in its immediate neighbourhood. They are most frequent on the outer slopes of the swelling or just beyond it; only in very severe cases are they found at any great distance from it. They are seen most frequently as scattered red corpuscles lying along and amongst the nerve-fibres (striate hæmorrhages). In specimens stained by Cajal's method it can be seen that the nerve-fibres generally remain normal, and are merely separated by the extravasated blood; but in and around

larger hæmorrhages they often present the degenerative changes dealt with later.

Frequently the hæmorrhages raise the membrana limitans interna from the nerve-fibres, in one case to a height exceeding that of the

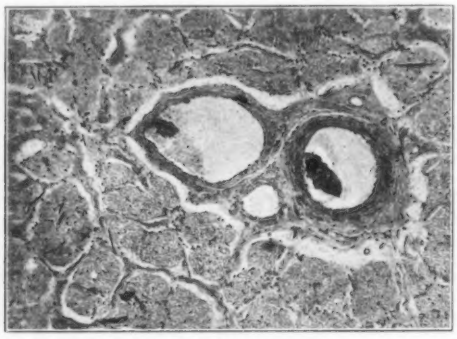

FIG. 10.

Cross-section of the central vessels in the centre of the nerve immediately before the exit of the vein, showing vein fully distended.

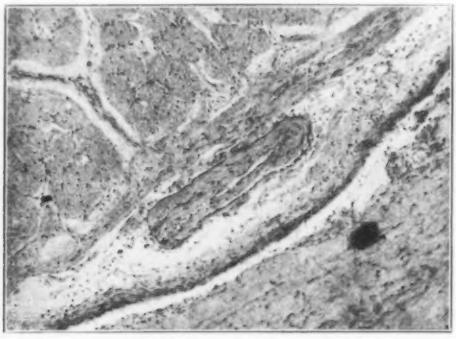

FIG. 11.

Section of the same vein in the subarachnoid space.

whole retina. These blot hæmorrhages resemble the œdema vesicles in that they are most frequent on the macular side of the disc, but they may occur anywhere on or around it.

Hæmorrhages also occur in the outer molecular layer just beyond the retinal folds. In the other retinal layers they are less frequent,

and when present are mostly due to extension from the nerve-fibre layer or outer molecular layer. A considerable number of red blood cells are commonly found in the subretinal exudate.

While the hæmorrhages are chiefly due to the venous congestion it is probable that another factor plays at least some part in their causation. An abrupt fungiform swelling of five or six dioptres must cause great mechanical stretching of many of the smaller vessels, and consequently produce a liability to rupture. The fact that the most frequent site of hæmorrhage is on or just beyond the downslope of the swelling seems to indicate that this is at least a factor in producing the hæmorrhages.

The vascular changes that occur in the later stages of papillœdema are most obvious in the papilla. The capillaries and smaller vessels, which in the earlier stages are engorged, become occluded by endothelial proliferation (fig. 16). The adventitial sheath of the larger vessels becomes considerably thickened and occasionally undergoes a form of hyaline degeneration. These vascular changes, which can be best interpreted as the results of an earlier congestion, extend down to the lamina cribrosa, but in the nerve behind this they are not so marked and may be absent.

There was no evidence of any general choroidal congestion: in a few cases there was a slight congestion of the choroidal veins in the immediate neighbourhood of the disc, probably due to their anastomosis with the engorged vessels in the anterior part of the lamina cribrosa.

C. Inflammatory changes.—Various writers on papillœdema describe inflammatory changes as the essential and characteristic feature of the condition, while others have found no evidence of inflammation in the majority of the cases they have examined. This discrepancy must be evidently largely due to differences in the conception of what the term inflammation connotes; some definition is consequently necessary, or rather a statement of the histological changes that can be accepted as indicative of it.

The usual definition of inflammation is the reaction of irritated or damaged tissues that still retain vitality. The histological changes that constitute this reaction are an active engorgement of the vessels, an exudation of fluid into the affected tissue, an infiltration of leucocytes, combined with proliferation of certain fixed tissue cells, and invasion and multiplication of wandering cells. In inflammation of long standing or of low grade, one or more of these features may be absent.

In the nervous system, however, inflammation shows certain

peculiarities, as the structures of epiblastic origin—i.e., the functional elements and the neuroglial supporting tissues—do not take an active part in the process, which is consequently limited, at first at least, to mesoblastic tissues, that is, the blood-vessels and the little connective tissue they carry with them from the leptomeninges.

Not only is the constituent portion of the nervous system that is involved by inflammation thus very small, but there is also a remarkable independence of the epiblastic and mesoblastic portions in pathological processes, so much so that Nissl and others assume a hypothetical *Grenzmembran*, or frontier between them, through which a pathological process does not readily break.

This relation explains the fact that in slighter inflammation the characteristic histological changes are entirely limited to the vessels and the connective tissue that surrounds them, and that only the destructive effects that accompany or result from it are visible in the nervous tissue itself. If, however, these destructive changes become more intense, the cellular infiltration that had been hitherto perivascular may break into the epiblastic tissue. On the other hand, the fluid exudate may, at an earlier stage, or in slighter degrees of affection, percolate the nervous tissue itself.

Long-standing œdema of any tissue, especially when it produces degenerative or destructive changes in the parenchyma by mechanical distension or nutritional disturbance, may lead to a thickening of the vessel walls and of the supporting matrix, and even slight cell infiltration, which may be easily confused with an inflammatory process, or a secondary inflammation of low grade may occur. Thus, even when inflammatory changes are present, it must be decided whether they are primary or secondary.

The chief change that we have observed in the nerve-head or retina in optic neuritis that can be interpreted as evidence of inflammation is a slight small round cell infiltration into the connective tissue sheath of some of the vessels. This is always small in amount when it does occur, and is generally present around only one or two vessels in any disc. It is most commonly seen in the loose connective tissue around the first branching of the central vessels, but it occasionally extends some distance along one, or a few of the branches. We have also seen it in the adventitial sheaths of the vessels as they pass through the lamina cribrosa, but very rarely round the central vessels in the retrobulbar portion of the nerve. We did not find any trace of infiltrating cells in the septa of the nerve.

These infiltrating cells, when present, lie in the sheath itself, apparently in the Virchow-Robin space; they are never actually perivascular. They are always of the small lymphocyte type, though we occasionally saw cells with similar nuclei but surrounded by more cytoplasm in the loose and œdematous tissue around the central vessels. We never recognized any polymorphonuclear cells or definite plasma cells among these lymphocytes.

Though practically all our optic discs were examined in almost serial sections, we never observed this cellular infiltration spread or break from the perivascular connective tissue into the parenchyma; and we have nowhere found any cellular infiltration among the nerve-fibres, or elsewhere in the nerve or retina.

As a rule there is no noteworthy proliferation of the fixed tissue cells of the adventitial sheath associated with the small round cell infiltration, but the fact that in the later stages of the neuritis, or in discs in the state of consecutive atrophy, there is an increase of perivascular connective tissue, makes it imperative to regard some of these cells as fibroblasts.

This small round cell infiltration was present in only a relatively small proportion of our cases—in less than a quarter. Further, it was found only in cases of relatively long standing, in which the papillœdema had been intense. This, combined with the fact that when present it was generally surprisingly local, and could be often seen around only one or two small vessels in a disc, makes it impossible to assume that it constituted the primary pathological process. On all these facts it appears much more probable that, even if accepted as evidence of inflammation, these locally restricted changes represent only a reaction of the tissues to the degenerative and destructive effects which result from some other pathological process.

The only other histological changes we found that could be interpreted as inflammatory were the vascular engorgement, the œdema, and the degenerative changes in the nerve-fibres; these changes can be, we believe, more satisfactorily regarded as non-inflammatory in their origin.

Certain authors, as Liebrecht [35], Elschnig [15], and Lawford and Edmunds [32], have described as an important pathogenic factor in optic neuritis a perineuritis of the nerve-stem, from which the inflammatory process invades the nerve and produces therein certain degenerative changes. This term can only mean a meningitis of the pial sheath, and of this there was no trace in any of our cases, excepting in those of

general meningitis in which the disease had spread into the optic sheath. The probable effect of such a perineuritis or meningitis on the optic nerve, if it did exist, can be best estimated by analogy with the changes a local or a general meningitis evokes elsewhere in the nervous system in the underlying tissue. And it is now generally recognized that a surprising feature of meningitis is the little change that may occur here, for as a rule the inflammatory cell infiltration does not break through the pia mater. If it extends inwards it is only along the vessel sheaths; and it produces at the most a superficial œdema of the brain, and frequently even this is absent or very slight. A meningitis that can produce it must be infinitely more intense than has been described or figured in the optic sheath by the authors who have postulated this as a causal factor of papillœdema.

The fact that in some of our cases of meningitis, in which the inflammatory processes extended into the optic sheath, the ophthalmoscopic and histological features of the disc changes were identical with those of tumour papillœdema, make it improbable that even in this small group the perineuritis which existed could have contributed to its pathogenesis.

It appears to us that a strong argument against the views of those who assume a "descending inflammation" or an inflammatory perineuritis as a casual factor in papillœdema is the fact that acute and extensive inflammatory lesions may exist in the optic nerves, as in a case we examined, and yet produce no trace of optic neuritis; in fact it is only rarely that retrobulbar neuritis produces any swelling of the nerve-head; and then only when the inflammatory focus lies in the nerve near the bulb.

We have had the opportunity of examining histologically such a case of retrobulbar neuritis, which had been observed from its commencement by one of us.

K. P., aged 35. In September, 1908, following an operation on the right turbinate bones, there was infection of the right sphenoidal sinus. Three days later she developed a large absolute central scotoma of the right eye, and the characteristic signs of retrobulbar neuritis. The disc and fundus presented no abnormal changes. Within two months there was a considerable recovery of the periphery of the field, but a small central scotoma remained; the disc had become pale, and its vessels small. In the beginning of February, 1909, she suddenly developed signs of an acute meningitis which led to a fatal termination five weeks later. To the end the right papilla showed no trace of swelling, but

only the features of a primary atrophy; but a definite papillœdema of the left disc developed. *Post-mortem* examination revealed a general pneumococcal meningitis, most intense on the base of the brain.

Microscopical examination of the left eye showed an early papillœdema, while in the right eye, though there was an inflammatory lesion in the nerve near the foramen and small round cells in the sheath, there was no trace of œdema of the papilla, but only the histological features of a retrograde atrophy.

By the careful study of our sections we are forced to the definite conclusion that the histological characters of papillœdema, no matter in what stage of its development it may be examined, are not those of an inflammatory process. The indications of inflammation that are occasionally found in intense or prolonged papillœdema are such as only justify the assumption that if any true inflammation exists it is merely secondary to the disturbance produced by the œdema. Our material has been so large that we can only assume that the authors (Leber [33], Gowers [18], Deutschmann [10], Elschnig, [15 and 16] Lawford and Edmunds [32], &c.) who have described papillœdema as an inflammatory process have been misled by the histological appearances, and especially by mistaking proliferated neuroglial and other nuclei for infiltrating cells. If this glial proliferation be so misinterpreted its association with vascular congestion and œdema may easily lead to the erroneous assumption of an inflammation.

D. The nerve-sheath.—Considerable attention has been almost invariably paid by previous writers to the state of the nerve-sheath in papillœdema, and different pathological changes have been described within it. Like most of these authors, we frequently found considerable dilatation of the sheath, especially in that portion of it near the bulb, while posterior to the exit of the vessels and near the optic foramen it was less distended; consequently when the eye was carefully removed the sheath presented the contour of a leek, gradually becoming larger towards the bulb, but again suddenly constricted immediately posterior to it. Unhappily we have not detailed descriptions on this point made at the autopsy for each eye, and we are therefore unable to give the percentage of cases in which various degrees of this distension was present, and deductions on it drawn from fixed and hardened specimens would be evidently unreliable.

It seems, however, to have no constant or close relation to the stage or intensity of the neuritis, and is as marked in some of the early cases as in late cases of great intensity. The subarachnoid space is chiefly

distended, and when the dilatation is great the arachnoid is pressed against the dura mater; some strands remain attached to the pia mater, while others are probably ruptured. Usually this space contains no visible substance, but occasionally a coagulated exudate is visible within it, as though its fluid were more highly albuminous than is the rule. (It may be mentioned in this connexion that when cerebrospinal fluid is cut off from the general cerebrospinal circulation, as it may be in the lower portion of the spinal theca by a tumour, it often becomes so highly albuminous that it may undergo spontaneous coagulation [7 and 44].) In two cases there were small hæmorrhages in the sheath.

We observed no noteworthy changes in the dura mater, but there was frequently, especially in the more chronic cases, a considerable proliferation of the endothelial cells of the arachnoid, and even a thickening of its fibrillæ. There was, however, never sufficient thickening or contracture to threaten compression of the nerve.

In attempting to interpret the nature and origin of this change it must be remembered that even in normal specimens the development of the arachnoid varies considerably. The thickening is certainly not inflammatory, at least, it was not associated in any stage with any evidence of inflammation. The cellular proliferation is more probably a result of the distension of and stasis in the sheath, and the consequent nutritive disturbance. A similar thickening of the arachnoid is often seen over the spinal cord unassociated with inflammatory changes.

The pia mater usually presents no pathological changes, excepting the œdema of its inner layer which has been already dealt with. Small round cell infiltration was present in only one of the cases of tumour papillœdema we examined, and here there was only one small patch of infiltrating cells. No other definite evidences of inflammation were present in any of these cases.

In three cases of meningitis with papillœdema, one tubercular and two purulent, some of the characteristic infiltrating cells were present in the subarachnoid space of the nerve-sheath: in the tubercular case they were chiefly small mononuclear, large mononuclear, and large hyaline cells; in the purulent specimens polymorphonuclear cells. In fact, the meningeal change had extended to the optic sheath. Despite this, there was very little evidence of inflammatory changes within the nerve, though the subpial œdema was marked.

E. Degenerative changes. — The chief degenerative changes of papillœdema are limited to the functional tissue of the disc and nerve, that is, the nerve-fibres, while in the supporting tissues only secondary changes of a reparatory or sclerotic nature occur.

These changes in the nerve-fibres can be naturally divided into the *primary degenerations* that result directly from the pathological process, whatever it may be, or the mechanical or nutritive effects that it produces; and the *secondary or Wallerian degeneration* that occurs in the cerebralward portion of fibres, the continuity of which has been interrupted.

The primary degeneration is naturally most pronounced in the regions where we find the greatest disturbance of the nerve-fibres by the œdema and swelling, that is, near the surface of the swelling, and in the large lateral bulging of the nerve-fibres. But when there is much œdema these changes can be seen across the whole area of the disc (fig. 12).

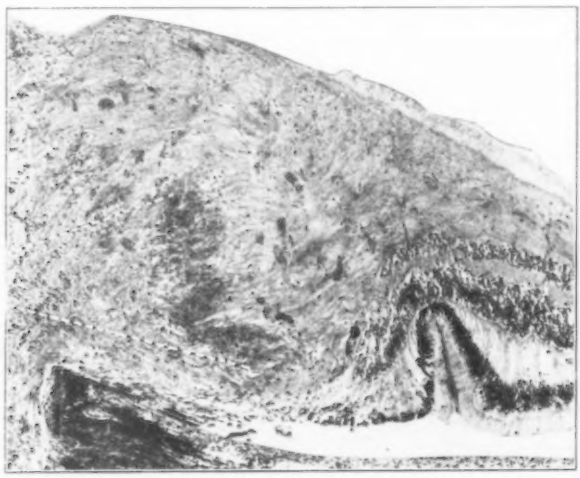

FIG. 12.

(From same case as fig. 4. different section under higher magnification.) Shows large area of degenerating nerve-fibres, *a*.

Their earliest appearance varies according to whether they occur where the fibres lie compactly arranged, or separated from one another by the œdematous fluid. In the former case, as among the intermediate fibres, ordinary hæmatoxylin and Van Gieson or eosin stained preparations occasionally show an area opaque and almost homogeneous in appearance, and on examination under higher magnification this is seen to be due to the tight packing together of swollen and varicose fibres. The enlargement and irregular contour of the individual fibres

is more easily seen where they are separated from one another by the fluid exudate, as in the lateral bulging that displaces the retina.

But as these nerve-fibres are naked axis cylinders, other methods are necessary to demonstrate accurately the changes they undergo; we consequently employed the methods of Cajal and Bielschowsky in the examination of six eyes, and by their aid, and especially by Cajal's method, it was easy to determine their exact nature. The swelling generally begins at one spot in a fibre, but there is often an irregular increase of its calibre over a certain length. It results from a local increase of the interfibrillar protoplasm which separates the fibrils from one another, as a rule in such a way that these seem to lie in the periphery of the swollen fibre (fig. 13).

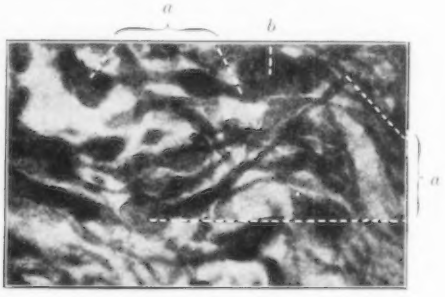

FIG. 13.

Preparation of nerve-fibres in disc, stained by Cajal's method. *a*, nerve-fibres showing varicosities and terminating in bulbous swellings; *b*, fully developed cytoid body at end of varicose nerve-fibre.

As the swelling increases in diameter the neurofibrils become disintegrated and disappear. From this stage these degenerative changes in the fibres develop rapidly, but in suitable preparations their evolution can be easily followed. As a rule, in a certain portion of the affected fibre the swelling increases and forms a spindle, continuous at each of its poles with the nerve-fibre, but as it increases further in diameter and becomes more globular it frequently loses its visible continuity with it, or a rupture occurs at its central end, so that it remains for a time attached only to the distal portion of the fibre on which it has developed (fig. 14). Often, however, they can be seen lying isolated in the nerve-fibre layer as more or less homogeneous colloidal bodies. Each contains, as a rule, at or near its centre, a core with a relatively sharp margin resembling a nucleus, but distinguishable

by its highly refractile appearance, its homogeneity, and its staining properties (fig. 15). In hæmatoxylin and Van Gieson preparations this core takes a brownish-violet tint, with Unna-Pappenheim's pyronin-methyl green mixture a bright pink, and with the reduced silver stains of Cajal and Bielschowsky a homogeneous black. None of the methods we employed revealed any structure within it. In shape, too, this core is often quite dissimilar from a nucleus; for instance, we have seen one extend into both, or lie between two, bulbar enlargements on a fibre, and occasionally one appears as an elongated cylindrical structure.

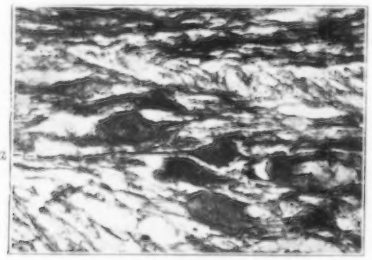

FIG. 14.

Nerve-fibres and cytoid bodies stained by Bielschowsky's method. *a*, a nerve-fibre continuous with a cytoid body.

The body is often somewhat rarefied or finely granular immediately around the core; in ordinary hæmatoxylin or aniline stained sections the rest is usually homogeneous, but in preparations in which the neurofibrils are stained it often appears finely granular, as if it contains the detritus of the disintegrated fibrils, and occasionally a trace of meshwork appearance is seen as though the neurofibrils had not completely broken up.

These structures are evidently the so-called "*cytoid bodies*" frequently described in the retina in pathological conditions, especially in albuminuric retinitis, vascular lesions, and in the neighbourhood of local injuries. They have been carefully studied in the latter condition, especially by Tepljaschin [60] and Parsons [48]. We compared those that occur in the two former states with those we found in papillœdema, and were unable to detect any essential difference between them. They have been previously described in papillœdema by several writers. They are most frequently seen near the apex of the swelling, or in the lateral bulge of the papilla, but can be found in practically every part

of the disc; in very few cases, however, are they situated near the main mass of the lamina cribrosa, or behind the level of the choroidal angle, and in papillœdema they rarely lie far beyond the margin of the disc. They occur only among the nerve-fibres, and never in the nerve behind the lamina cribrosa.

We have devoted a considerable space to the description of these bodies, as it is unquestionably they that have been recently described as macrophages [27], though they have been generally regarded as degenerated nerve-fibres, or *varikös-sklerotische Sehnervenfasern* (*cf.* figs. 15 and 17).

Our observations confirm unequivocally the latter view, and so many different arguments support it that it appears to us to be beyond doubt. The danger of confusion can exist only when the fully developed cytoid

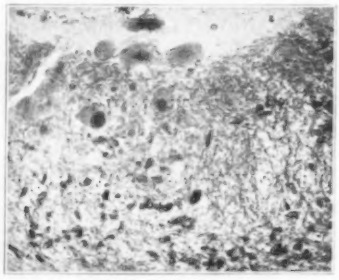

Fig. 15.

Cytoid bodies lying free near the surface of the disc (stained by hæmatoxylin and Van Gieson's stain).

bodies are studied by inadequate methods, but though these may have a superficial resemblance to cellular structures their cores have neither the histological characters nor the staining properties of the nuclei of any variety of cells that are found in the eye or in the nervous system, in either normal or pathological conditions. The fact that they occur only in the nerve-fibre layer is also strongly in favour of their origin from nerve-fibres. Further, as we have already described, it is frequently easy to see in even ordinary preparations that in the early stages of their development at least they are continuous with nerve-fibres, and their relation to the fibres, and their mode of development from them, may be more definitely determined in discs treated with the specific axis-cylinder methods of Cajal and Bielschowsky. By both these methods the cytoid bodies take the same colour as the normal

axis-cylinders, even when we cannot demonstrate their continuity with these.

Finally, we treated one eye by Donaggio's method, by which only recently degenerated fibres are stained, and the rest of the section remains colourless; in this eye only the cytoid bodies were coloured. In another eye that had been fixed in Müller's fluid and stained by Weigert-Pal's method, the earlier cytoid bodies contained blue granules, while in those in the later stages of development the granules were a brownish-yellow.

These various arguments, we believe, leave no doubt that these so-called cytoid bodies represent portions of degenerated nerve-fibres, and are not macrophages, as they have been recently described, nor degenerated leucocytes, as Litten [37] and Greeff [22] believed.

Cytoid bodies are rarely found in the later stages of papillœdema when it has subsided into atrophy. Their disappearance can be readily observed in suitable preparations: they first become pale and more globular, and in such a disc treated by Marchi's method coarse and irregular fat globules are found within the clumps, and even within the cytoids themselves. Thus they evidently undergo a fatty or lipoid degeneration when they reach a certain stage of development, as Parsons has already shown. It appears probable, though we cannot make the statement with certainty, that they all disappear by undergoing this type of degeneration.

This varicose swelling of the nerve-fibres and the ultimate development of cytoid bodies from some of them was the main degenerative change we observed in the disc. As its nerve-fibres are naked axis-cylinders the Marchi method naturally revealed no change beyond the lipoid degeneration of the cytoid bodies.

The immediate cause of this form of degeneration must be briefly considered. There are evidently three possible pathogenic factors: the first is the stretching and tension to which the nerve-fibres are subjected owing to their displacement by the œdema; secondly, it may be due to imbibition by the fibres of the œdematous fluid in which they lie; and finally, it may result from the nutritive and circulatory disturbances, that result directly from the œdema.

It is not possible to exclude the latter two factors, but certain observations make it very probable that the stretching of the fibres owing to their displacement has a very important influence. In the first place, as we have already described, this varicose degeneration of the fibres occurs most commonly where these are subjected to the greatest tension,

i.e., on the surface of the disc and in its lateral bulging; but a more important observation which we could repeatedly make was the fact that where a bundle of fibres was held back by, and consequently bent at an angle over, a vessel or a band of supporting tissue, these portions of the fibres, and most frequently that lying on the central side of the obstruction, presented this change (fig. 16). This was generally so remarkably local that there can be no doubt that the pressure and the stretching of the unsupported portions of the fibres was an important factor in its causation. On the other hand, this form of degeneration may be found

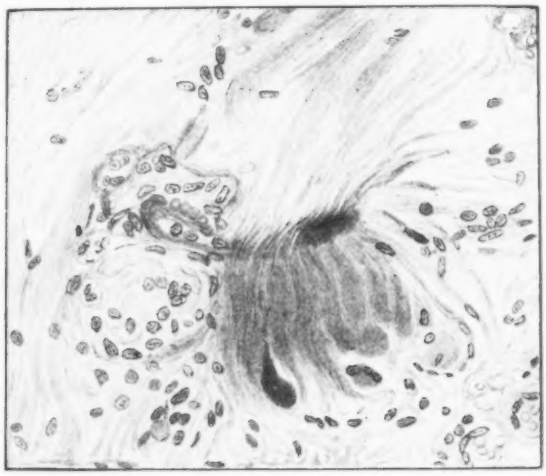

FIG. 16.

(Drawing.) Shows a bundle of nerve-fibres held together by small blood-vessel and bent over it; development of varicosities and cytoid bodies on central side of obstruction. Shows also endothelial proliferation in walls of smaller vessels.

in places, as in the centre of the disc or immediately in front of the lamina cribrosa, where the nerve-fibres cannot be subjected to much local tension. The frequent occurrence of cytoid bodies in the neighbourhood of hæmorrhages, by which the fibres had been probably damaged, and as we have been able to observe in other cases, in the neighbourhood of vascular occlusions, and in albuminuric retinitis, makes it impossible to assume that such local stretching is always the main cause of the degeneration; it would probably be more correctly regarded as a predisposing factor.

The neuroglial elements of the disc and retina do not suffer degener-

ative changes; but swollen neuroglial cells with pale or granular cytoplasm (*Körnchenzellen*) may be seen in the œdematous areas of the nerve-fibre layer.

On treating the retrobulbar portion of the optic nerve by Marchi's method, as we did in a few cases, two distinct types of change were found. The first was represented by fatty globules stained black by this method arranged along the course of the fibres; this evidence of secondary or Wallerian degeneration was very uncommon, as might be expected, as at the most only a small proportion of the fibres can be interrupted in their course. The second type was represented by fine granules, often dark brown instead of black, scattered diffusely throughout the cross-section of the nerve, and not arranged in chains along the course of the fibres. Elsewhere in the central nervous system this appearance is taken as an indication of a primary diffuse degenerative change in the myelin sheaths due to toxic or nutritive causes, and it seems to us most probable that it was of this nature in the optic nerve also, and that it resulted from the nutritive or circulatory disturbances. In the latter stages of papillœdema we were able to demonstrate a degeneration or atrophy of bundles of fibres in the nerve by Weigert's method. The affected bundles generally occupied a crescentic area on one side of the nerve, and it was often possible to trace the continuity of these atrophied fibres with those most involved in the lateral bulge.

No prominent degenerative changes could be observed in the retina during the acute stages of papillœdema, though there might be a local destruction of certain elements of any layer by hæmorrhages or by the tension they are subjected to by the folding or swelling of the retina near the papillæ. In or around the site of such a hæmorrhage large inflated cells, which evidently act as scavengers or macrophages, could be observed (fig. 17). As the greater part of our material was obtained some hours after death, it is difficult to make a positive statement on the affection or escape of the rods and cones, but in freshly obtained material we could detect no definite evidence of degeneration of them.

In the stage of atrophy the ganglion cells are considerably diminished in number, and those that remained are often shrunken in size; we have not, however, observed any acute degeneration of these, and from their appearance conclude they have merely undergone the secondary atrophy which supervenes in the cells of central nervous system when the fibres that spring from them degenerate.

F. Sclerotic changes.—An optic disc in the state of atrophy consecutive to a papillœdema is characterized by general shrinkage and

a diminution in the number of its nerve-fibres, combined with a proliferation of neuroglial nuclei, and an increase of the neuroglial fibrils that form its matrix. In addition, there is generally an increase of the connective tissue that surrounds the vessels.

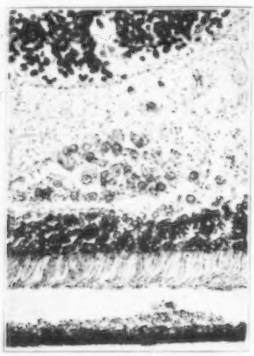

FIG. 17.

(From same section as fig. 15.) Macrophages in the site of an old haemorrhage in the outer molecular layer. (Note the difference in the appearance of nuclei from the core in the cytoid bodies in fig. 15.)

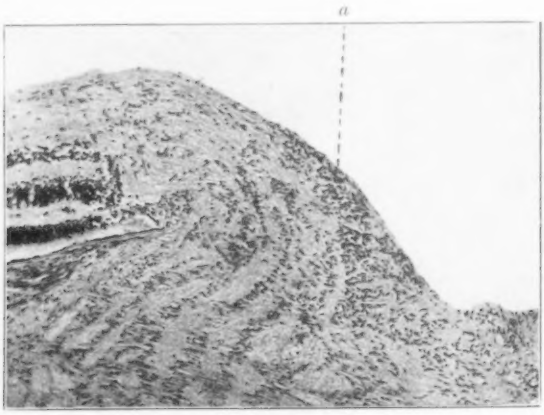

FIG. 18.

Subsiding neuritis with commencing sclerosis. *a*, proliferating neuroglial nuclei.

The development of these changes can be followed from the time in which there is yet considerable swelling of the papilla. Their earliest evidence is a proliferation of the neuroglial nuclei, visible

first, as a rule, near the apex of the swelling around the central pit. This neuroglial proliferation coincides with the diminution of the œdema and soon gives rise to a prominent mass of nuclei in this region (fig. 18). The nuclear proliferation apparently occurs by direct division, and these nuclei are distinguishable from the normal neuroglial nuclei of this region only by their slightly greater size, and by the coarser chromatin granules they contain. It is followed by an increase of the neuroglial matrix, the fibrillæ of which are definitely coarser than normal.

FIG. 19.

Advanced post-neuritic atrophy with marked neuroglial sclerosis.

About the same time, or later, a similar proliferation of the nuclei and fibrillar elements of the neuroglia can be seen in the lateral portion of the disc among the distorted nerve-fibres that displace the retina. Here it generally occurs first in and around some of the bands of supporting tissue that are drawn outwards, and often there results an islet of sclerotic tissue that lies in or on the inner side of the main mass of the lateral bulging. At a somewhat later stage, as the œdema subsides, this neuroglial sclerosis spreads over the rest of the disc; it first becomes apparent by the increase of the nuclear columns that lie between the bundles of fibres after these have passed through the lamina cribrosa (fig. 19).

As it becomes general throughout the disc this neuroglial sclerosis

rapidly leads to shrinkage, at least in cases in which there has been considerable œdema and destructive change. A noteworthy result of this shrinkage is that, by it, the retina that had been displaced outwards by the œdema is again drawn in, and occasionally in much atrophied discs beyond its normal limit. This shrinkage probably produces a degeneration or rather an atrophy of nerve-fibres that have hitherto escaped damage; at least, there can be no doubt that the diminution in the number of fibres in the stage of atrophy is always much greater than that which we have ever seen in a disc in which the œdema and consequently the destructive processes are subsiding, but in which sclerosis had not yet become pronounced.

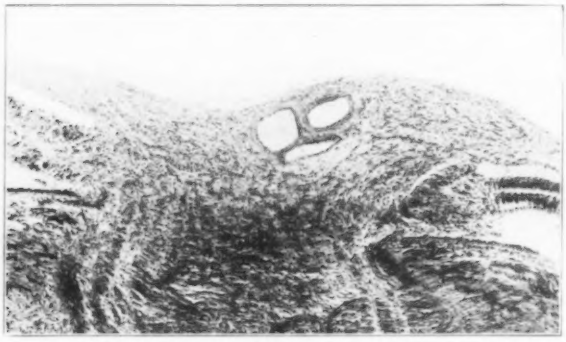

FIG. 20.

Section from same case as fig. 19, under a lower magnification, to show the thickening of the lamina cribrosa.

The neuroglial sclerosis in the stage of atrophy leads to a noteworthy change in the histological appearance of the disc, as it obliterates the normal striate appearance of vertical sections, which is due to the course of the nerve-fibres or of their bundles parallel to one another.

This coarse neuroglial sclerosis generally extends only a short distance from the disc into the nerve-fibre layer of the retina.

As we have had the opportunity of examining eyes in which the papillœdema was relieved by a cranial decompression and *had* subsided without serious deterioration of vision ensuing, their histological appearances may be contrasted with those in which secondary atrophy had supervened. In a few of these cases, though intense papillœdema had existed, the histology of the disc and retina was practically indistinguishable from the normal; in other cases the only noteworthy

deviation from the normal was the existence of a slight sclerosis in the regions of the disc in which the sclerosis as a rule commences (fig. 18).

From its character, as well as its mode of development, there can be no doubt that the neuroglial sclerosis of the atrophying papilla is purely secondary to the damage produced directly by the œdema, and to the mechanical and nutritive disturbances it occasions.

The main part played by the mesoblastic tissues in the sclerosis of an atrophying disc is a thickening of the outer sheaths of the vessels; no new connective tissue is laid down elsewhere in the disc. A considerable thickening of the main mass of the lamina cribrosa is often apparent in the later stages of papillœdema, and especially in advanced atrophy (fig. 20).

The degeneration or atrophy of bundles of nerve-fibres in the optic nerve in the later stages of papillœdema is followed by a characteristic secondary neuroglial sclerosis, with an increase of both the nuclear and fibrillar elements, within and around them. It is generally accompanied by a thickening of the connective tissue septa of the nerve; this, like the neuroglial sclerosis, is purely secondary to the degeneration, and we never obtained any evidence that it was preceded by or resulted from an inflammatory process.

The Nature of Tumour Papillœdema.

The careful examination of the material at our disposal permits us to express a definite opinion on the nature of optic neuritis.

The essential change, as we have described, is an œdema that separates the nerve-fibres in the disc and its neighbourhood, but rarely invades the retina; it produces the swelling and the other characteristic ophthalmoscopic features. The hæmorrhages that occur are partly due to the stretching and rupture of the small capillaries that are involved in the swelling, and partly to the associated venous engorgement.

On the other hand, in the great majority of our cases there was no evidence of any inflammatory process in the papilla or in the optic nerve, and in those in which there was a slight round cell perivascular infiltration this was evidently a secondary process.

Further, the degenerative and atrophic changes that occur in the nerve-fibres and ganglion cells can be best explained as secondary to the œdema.

We therefore conclude that "optic neuritis," or "choked discs," as it occurs in association with conditions of increased intracranial pressure, is in its essential nature an *œdema*.

The Correlation of the Ophthalmoscopic Appearances and the Histological Changes.

As with one exception the fifty eyes we examined were observed ophthalmoscopically during life, and many of them repeatedly, we can with some assurance attempt to correlate the ophthalmoscopic features of papillœdema with their underlying histological changes.

The hyperæmia of the discs in the early stages is evidently due to congestion of the smaller veins and capillaries in the disc itself and in the anterior layers of the lamina cribrosa. The blurring of the edges of the disc and their subsequent obscuration, as well as the burying of the vessels in part of their course, is partly a result of the increased depth of the tissue, and partly due to the dispersion of light by the œdematous fluid in the tissue, just as opacity of the lens is produced by separation of its fibres by drops of fluid. The tortuosity of the veins is mainly due to their congestion, but the swelling displaces the vessels in a plane vertical to the retina and so increases the apparent waviness of their course.

The fine greyish-white striate appearance of the disc and the neighbouring retina, especially along the vessels above and below the disc, is due to a separation of the nerve-fibres by œdema.

The striate or flame-shaped hæmorrhages are those that lie in the nerve-fibre layer and spread along the fibres; while the conspicuous "blot hæmorrhages" that occur, especially on the slope of the swelling, lie under the membrana limitans interna and separate it from the nerve-fibre layer. The less conspicuous rounded hæmorrhages lie in the deeper retinal layers, especially in the outer molecular layer.

The soft white patches of irregular shape on and in the neighbourhood of the disc, and the white stippling of the disc, are produced by the swelling of the nerve-fibres, the formation of cytoid bodies, and their fatty and other degeneration products.

The greyish-white lines that run concentric with the outer edge of the disc are obviously due to the retinal folds, their presence being occasionally accentuated by hæmorrhages lying within them.

In severe cases the retina on the macular side of the disc is swollen and greyish, owing to its œdema.

Occasionally the difference in level between the retina on the inner and the outer sides of the macula may amount to three dioptres. The faint greyish striation radiating from the macula that may be seen in these cases is due to the œdematous separation of the nerve-fibres, while the macular fan of bright white discrete spots that often develops later

is due to the superficial vesicles which are formed by the raising of the membrana limitans interna from the nerve-fibre layer. As we have seen, the distribution of these is determined by the short course of the macular fibres and their anatomical arrangement. As the papill-œdema subsides the macular fan may disappear and leave not a trace behind.

The opaque white appearance of the atrophic disc is produced by the diminution of the vascular engorgement, the occlusion of the smaller vessels, and the glial and connective tissue sclerosis. The shrinking of the sclerosing tissues pulls back the retina into position, and the only sign of its displacement left may be some disturbance of the pigment round the disc. The white lines along the larger veins in the neighbourhood of the disc are due to the thickening of their walls, and the diminution in the size of the arteries is brought about by their compression in the sclerosed tissues.

Comparison of Tumour Papillœdema with the Pathological Changes in Similar or Allied Conditions.

(1) *Meningitis.*—We have examined the papillæ and optic nerves in three cases of meningitis (one tubercular and two septic), in which there were the ophthalmoscopic appearances of papillœdema. We have not included these cases among those of tumour papillœdema, as the local infective and inflammatory process might be possibly an additional factor in the pathogenesis of the condition, or might modify the characteristic histological changes and thus give rise to confusion. There was, however, no essential or even visible difference between the histological changes in these cases and in those of tumour papillœdema, and in them there was as little evidence of inflammatory changes in the papilla as in the latter group. Even though the meningeal infiltration extended to the optic sheath there was no inflammation of the enclosed nerve; this, indeed, might be expected, as even in the superficial layers of the cerebral cortex remarkably little change, apart from œdema, results from meningitis, unless the latter be very intense.

We can therefore conclude that the papillœdema that occurs with meningitis *need* not be inflammatory in origin, but may be dependent, like tumour papillœdema, on the increase of intracranial pressure.

(2) *Retrobulbar neuritis.*—Definite œdema and swelling of the papilla

and other signs analogous to those of tumour papillœdema may occur in retrobulbar neuritis, but probably only when the lesion lies near the bulb. Unfortunately we have not had the opportunity of examining such an eye, but we have studied for comparison an eye in which this condition existed without primary papilla changes.

This case, in which the retrobulbar neuritis was due to septic extension from the sphenoidal sinus, has been already referred to. The lesion lay near the foramen, and had at the time of death produced an extensive degeneration of the nerve, but the inflammatory changes had not spread into its distal portion, nor into the papilla.

This case is instructive in showing that local inflammatory lesions of the optic nerve itself *may not* give rise to a descending neuritis, a perineuritis or an inflammatory papillitis. In fact, from general experience there seems to be little tendency for inflammatory processes in the nerve to extend to the papilla unless they lie in its immediate neighbourhood.

We have also examined a case in which a basal tumour compressed the one optic nerve before its exit through the optic foramen, and produced a retrograde atrophy of the nerve-fibres and ganglion cells, and sclerosis of the nerve and disc. There was, however, no œdema, round cell infiltration, or other evidence of inflammation in the intra-orbital portion of the nerve or disc, despite the local lesion. In the other eye of this case there was typical papillœdema; it is included among our cases.

(3) *Albuminuric neuro-retinitis.*—There is usually little difficulty in distinguishing ophthalmoscopically between neuro-retinitis of renal or other origin and tumour papillœdema, but occasionally it is not easy to do so. It is consequently interesting to compare the pathological changes in the two conditions.

We have examined three eyes from cases of Bright's disease in which there was marked ocular change. There was no papillœdema in either eye of one case, but in the other the disc subsequently examined was swollen to the height of five dioptres.

An affection of the retina was the most prominent histological feature in all three eyes.

In two of these eyes in the nerve-fibre layer there were large areas of swollen and degenerated fibres, many over a disc-breadth in diameter, and often so close together as to be almost continuous; in many the layer was swollen to double its normal thickness. These areas were made up of varicose nerve-fibres and cytoid bodies in various stages of development, and often contained fatty or calcareous degeneration products,

and in some cases the traces of older hæmorrhages. The membrana limitans interna was usually raised from their surface, and in some of the smaller foci from which the degeneration products had disappeared it formed the roof of a cavity which was crossed only by the fibres of Müller. The ganglion cell layer and even the inner molecular and nuclear layers were often destroyed below these areas of nerve-fibre degeneration.

In other places the ganglion cells were diminished in number and replaced by rows of proliferating neuroglial cells which had often a considerable quantity of cytoplasm. The inner molecular and inner nuclear layers, apart from the areas of destruction mentioned above, did not show much obvious change, except a little vacuolation of the inner nuclear layer in the vicinity of the disc. The outer molecular layer, on the other hand, was the site of very extensive change. Its fibres were pushed apart and had left large vacuoles, in many of which lay shrunken coagula; others were filled in by a reticulum of fine fibrils, and in some there were the remains of old hæmorrhages. This layer also contained large globular cells with small nuclei and granular protoplasm, which were obviously macrophages. The outer nuclear layer did not present much alteration except where the œdema from the outer molecular layer had spread into it, or where the subretinal exudate had burst through the rod and cone layer. The rods and cones were fairly well preserved on the inner side of the disc and also on the outer side beyond the macula, but in the neighbourhood of the macula where there was much subretinal exudate they were completely disintegrated, and the membrana limitans externa was destroyed. The layer contained numerous corpora amylacea. The pigment layer was on the whole normal. The adventitia of the vessels was thickened and hyaline, and the intima, especially in the smaller vessels, had proliferated so much that in many the lumen was completely obliterated.

The changes were quite as prominent in the choroidal vessels as those in the retinal, the arterial walls were specially thickened, the adventitia more than the intima. The choroid as a whole was diminished in thickness.

In the eye in which the disc was swollen the papillary changes differed in some respects from those seen in tumour papillœdema. The separation of the fibres of the lamina cribrosa was not so great, and the bulging forwards of its anterior layers was consequently only slight. The swelling mainly affected the nerve-bundles in front of the lamina cribrosa. The retina on either side was very much folded, and the

space under the folds was filled with exudate. The walls of the vessels in the nerve were thickened, and either the central artery or a large branch was thrombosed. This thrombosed vessel could be traced from outside the nerve-sheath into the centre of the nerve. The general retinal changes were similar, but the patches of swollen nerve-fibres and cytoid bodies were much smaller and more scattered.

The results of our examination of these cases support the view that the retinal changes in Bright's disease are due to the direct action of the toxins on the walls of the vessels, and especially on the capillaries. The fact that the outer molecular layer, in which Müller originally showed that the terminal anastomosis of the capillaries occurs, was the most severely affected is a strong point in favour of this hypothesis.

(4) *Arteriosclerosis.*—In the course of our investigation into the nature of the changes in the nerve-fibre layer, we had occasion to cut sections of two eyes in which there was marked retinal arterial degeneration.

In the one case, though there were marked silver wire arteries, there was no evidence of complete blockage in any of them. On section the arteries showed intimal proliferation with thickening of the media. There was no pathological change in the disc itself, but along the thickened vessels which stood out conspicuously on the retina there were patches of cytoid degeneration of the nerve-fibre layer.

In the second case the upper artery was completely blocked and was represented ophthalmoscopically by branching white streaks running into a large whitish area. There was marked sclerosis of all the other vessels, and numerous patches of œdema and degeneration in the retina, with a star-shaped figure at the macula. Practically the whole nerve-fibre layer in the area supplied by the thrombosed vessel was degenerated and thickened to at least three times the normal. The thickened areas contained cytoid bodies in all stages of formation with fatty and calcareous degenerative products. Over them the membrana limitans interna was raised by exudate, only remaining attached at a few spots. In other places it was normal in position. In the affected areas of the retina the outer molecular layer contained large vacuoles, many with shrunken coagula and others with remains of old hæmorrhages. The choroid underlying the affected area was very much thicker than normal, owing mainly to the great distension of its veins, while the only change in the arteries was a thickening of their walls.

This great choroidal distension was not present under the unaffected parts of the retina.

These arteriosclerotic cases thus are quite closely allied to the albuminuric cases in their histological features, as they are ophthalmoscopically.

From the histological description it will be seen that renal and arteriosclerotic retinitis differ in their most essential features from tumour papillœdema. In the one class there is essentially a simple œdema of the papilla, and the retina is involved only to a slight extent: in the other the retina is obviously the part principally and most seriously affected.

The Pathogenesis of Papillœdema.

It is not our intention to review in detail all the hypotheses that have been brought forward from the time of von Graefe to explain the occurrence of papillœdema in association with cerebral tumours. Some of them are based on assumptions which further investigations have proved to be far from justifiable; others are inconsistent with the facts which histological examination reveals. It is, however, essential to our purpose to refer briefly to some of the more important, and to discuss more fully the explanation which seems to us most consistent with all the clinical and histological features of the condition.

The hypotheses of previous writers may be conveniently divided into four groups:—

(1) Those that regard papillœdema as an inflammatory process (Leber [33], Gowers [18], Lawford and Edmunds [32], Deutschmann [10], Elschnig [15], Szimemi [59], and others).

(2) Those that assume that it is due to œdema propagated from the brain, in which it originally resulted from the presence of a tumour (Parinaud [46], Uhlrich [61], Sourdille [58], Kampherstein [31]).

(3) The hypotheses that attribute the swelling of the disc to a disturbance of the vasomotor innervation of the retinal vessels (Hughlings Jackson [28], Benedict [5], Adamkiewicz [1], and Loring [38]).

(4) The mechanical theories that regard the rise in intracranial pressure as the main factor.

(*a*) The original Schmidt-Rimpler [54] theory of direct driving of cerebrospinal fluid into the lamina cribrosa.

(*b*) That the disc changes are due to compression of the vessels as they pass through the lamina cribrosa or nerve (Manz [39], and Cushing

and Bordley [8]); or as they pass through the vaginal space or the dural sheath (Deyl [12], Dupuy-Dutemps [13], Merz [45]); or as the result of local vascular engorgement (von Graefe's original theory [23], and Judeich [30]).

(*c*) That the changes are due to a lymph stasis (Liebrecht [35] and Schieck [53]).

The inflammatory hypotheses must be decided mainly on histological evidence; our own observations, as well as those of many others (*e.g.*, Kampherstein), lend them no confirmation, as in the majority of our cases there were no inflammatory changes, and in the small percentage in which there was any evidence of inflammation it was slight in degree, irregular in distribution, and obviously secondary to some pre-existing change. Further, these inflammatory hypotheses are built on unproven assumptions, as the existence of toxins derived from a cerebral tumour (Leber and his school); or a descending neuritis or perineuritis of which no satisfactory evidence has been furnished, since the occurrence of inflammation even near a tumour is exceptional, apart perhaps from the infective granulomata.

The occurrence of a descending œdema spreading from the brain lacks proof, and no very satisfactory histological demonstration of its presence has been given. It is *a priori* improbable that œdema would spread over the long tract that must be traversed before it reaches the eye. Further, it is based on the assumption that a widespread œdema occurs in the brain when this contains a tumour, but long experience of pathological investigation of brain tumours has convinced us that such œdema occurs only in the immediate neighbourhood of a tumour, and is even here relatively rare.

According to Sourdille's hypothesis, fluid is forced from the third ventricle over the chiasma and thence into the optic nerves, which are therefore, owing to their swelling, strangulated in the foramina; as a result, venous and lymph stasis in the papilla and nerve ensues.

For the vasomotor theory there has been adduced neither experimental nor pathological support. Even if a vasomotor innervation of the retinal vessels exists, it is extremely improbable, no matter what its central connexion may be, that tumours, situated as they may be in any region of the brain, could disturb its functions so seriously as to produce an œdema of vascular origin.

Our observations establish the fact that papilloedema is an œdema of the nerve-head due to two factors—venous engorgement and lymph stasis. To understand the cause of the vascular obstruction to which

this venous engorgement must be due it is necessary to review the circulation of the blood and lymph in the optic nerve and retina, and the principles that determine and modify it. For various reasons this problem must be approached from its physiological rather than from its histological aspect.

The blood of the retinal circulation is drained by the vena centralis, the branches of which unite in the papilla and pass as a single trunk through the lamina cribrosa; here it has a limited anastomosis with the choroidal veins, and with the subpial veins of the nerve-stem, though probably no anastomotic connexion with the scleral veins corresponding

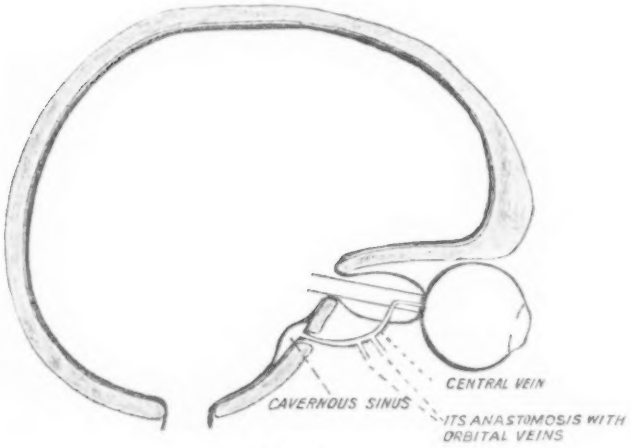

FIG. 21.

Diagram of connexions of central vein.

to the circulus arteriosus of Zinn (Leber) [34]. Behind the lamina the vein runs enclosed with the artery in a thick connective tissue sheath in the centre of the nerve. At a variable distance behind the bulb it bends out towards the pial sheath, and receives here tributaries from the pial veins. Occasionally it runs round the nerve under the pial sheath and then backwards for some distance in it: it then crosses the space of the sheath, unsupported, to reach the dura mater, which it penetrates more or less obliquely. In the orbit it usually joins one of the ophthalmic veins, generally the lower, and through them, or directly, enters the cavernous sinus. Through them, too, it communicates with the facial vein and with the pterygoid plexus.

The conditions under which the flow of blood takes place in the optic nerve are those which Leonard Hill [25] has shown to exist in the intracranial circulation. This must be so, for, as Schwalbe [57] has shown, there is a free communication between the nerve-sheath and the cranial cavity, and unless this is blocked pressure must be transmitted from the one to the other by the cerebrospinal fluid.

The normal intracranial pressure is determined by the venous pressure, and in pathological conditions can never exceed it, else the veins would collapse owing to the little resistance their walls can offer to compression. Similarly the blood-pressure in the cranial sinuses must rise parallel with the rise of intracranial pressure; the cavernous sinus is no exception, for though it may not be readily compressible owing to the support it receives from the recess in which it lies and the firm trabeculæ that traverse it, the pressure of blood within it must equal that of the petrosal sinuses into which it drains. An increase of the intracavernous pressure seems, however, to have little direct influence on that of the central retinal vein. V. Graefe, who originally suggested engorgement of the central vein, due to rise of the cavernous pressure, as the cause of papilledema, abandoned it when Sesemann demonstrated its free communication with the facial vein and the pterygoid plexus. But a stronger argument against this view is the fact that ophthalmoscopic changes occur in only a small proportion of cases of thrombosis of the cavernous sinus, and probably only in those in which the thrombus extends to the ophthalmic anastomosing branches (Uhthoff). It must therefore be concluded that the pressure of the vena centralis need not rise parallel with, or even in conjunction with, a rise of the cavernous sinus pressure.

It thus appears that the venous pressure in the retina and optic nerve is not *directly* dependent on the intracranial venous pressure, and may be little, if at all, influenced by it. But the intravaginal pressure rises parallel with the intracranial pressure, as there is a free communication between their spaces, and if the former is increased the pressure in the central vein must, by the same law that determines the cerebral venous pressure, rise to, or above, the same level if circulation is to be maintained within it. In its intraneural course the nerve, with its strong connective tissue septa, may prevent the sheath tension acting fully on the vein, but its intravaginal portion must depend almost entirely on its inside pressure to maintain its lumen; consequently here, at least, the venous pressure must equal that transmitted to the sheath from the cranial cavity. This rise of intravenous pressure must extend to all the

distal portions of the vein and its branches, as well as to the pial veins that drain into it, and all these must consequently become congested.

The pressure in the central vein of the nerve and in the pial veins cannot differ widely from the tension of the tissues in which they lie, as the latter, too, are subjected to the increased intravaginal pressure. But the effects of this cannot extend beyond the lamina cribrosa; therefore, as the pressure in the retinal veins and capillaries must rise parallel with that of the central vein, and as there is no increase of intra-ocular tension there arises a disproportion between the capillary and venous tension and the tissue lymph tension in the papilla. Under these conditions there must occur a venous engorgement which leads to an excessive lymph transudation. If the lymph drainage were unobstructed a permanent œdema of the tissue would not necessarily result, as the outflow might readily accommodate itself to the increased production. In cases of thrombosis of the central vein, for example, whether complete or partial, there is obstruction to the venous return, and consequently venous congestion, but as there is no obstruction of the lymph drainage there is little or no swelling of the disc. In this case we have the venous congestion acting without the second factor. But the lymph from the disc and nerve normally drains into the subarachnoid space of the sheath along the adventitial coats of the central vessels, and in the case of the nerve along the vessels that penetrate it from the pia mater; consequently any rise of sheath pressure must obstruct this outflow, and actually dam the lymph back until its pressure reaches the level of the intravaginal pressure. As the retina and optic nerve, like the rest of the central nervous system, have no proper lymph vessels, the tissues into which the lymph is transuded must distend until the pressure exerted in the stretching of them comes to equal that which obstructs the drainage of the lymph from them. When this point is reached a balance is established which will be maintained until an alteration takes place in one or other of the two forces; either the pressure in the sheath may be lowered (by trephining or when the communication with the intracranial cavity is cut off), or the development and contraction of cicatricial tissue in the disc may increase the power of the tissues to oppose distension. Even if the retinal lymph drain along the optic nerve directly into the intracranial cavity the same result must ensue, as the same raised pressure must block the outflow.

In our opinion therefore, the œdema of the papilla that constitutes tumour papillœdema is in the first place due to the venous engorgement that results from the rise of intravenous pressure that is necessary in

order that circulation should be maintained in the intravaginal portion of the vein where this is subjected to an increased sheath pressure. The increased sheath pressure is also the origin of the second factor, the obstruction to the lymph drainage from the papilla.

In other conditions, as orbital tumours and thrombosis of the cavernous sinus, a blocking of the venous return may be in itself sufficient to produce papillœdema, but as we have already shown, it does not necessarily do so.

It may be advanced as an argument against this theory, that cases of papillœdema have been described in which *post-mortem* examination revealed no dilatation of the dural sheath; the inference might be drawn that in these cases the intracranial pressure was not transmitted to the sheath. But such observations may be fallacious, as the cerebro-spinal fluid can escape readily after death, especially when the body lies on its back. Even in the cranium there is often no *post-mortem* evidence of an increased pressure that undoubtedly existed during life; and this is especially so when the examination is conducted a considerable time after death. Further, though the intravaginal pressure be raised, it need not necessarily distend a strong dural sheath.

Any pathogenic hypothesis must take cognizance of the cases in which papillœdema does not appear in one eye, or if already present subsides, when the pathological intracranial pressure is due to a tumour growing in the neighbourhood of the corresponding optic foramen. We have ourselves seen three such cases in which there was intense papillœdema in the eye of the side opposite to the tumour, but no disc swelling in the eye of the same side; and others have been recorded (Gowers [20], Schultz-Zehden [56], Judeich [30]). A tumour in this region may, directly or indirectly, block the communication between the intracranial cavity and the nerve-sheath, so that the increase of pressure in the former cannot be transmitted to the latter; our hypothesis demands that, as actually does occur, in these conditions papillœdema should not develop in the eye.

We can now consider the several other theories that are based on the assumption that a raised intracranial pressure is the primary causal factor of papillœdema. The majority of these assume an obstruction to the return of blood or lymph from the papilla, and seek to explain it.

Judeich [30] modified von Graefe's original theory with which we have already dealt. His own observation was made on a single case of septic thrombosis of the cavernous sinus. He assumes that the increased pressure of the cavernous sinus is propagated through the central retinal

vein to the veins of the nerve-sheath, which consequently become congested; a hydrops of the sheath results, and this causes a further pressure on the central vein. But, as von Graefe himself recognized, the pressure of the central vein need not rise parallel with that of the sinus, owing to its free anastomoses in the orbit. And the intravaginal pressure that would result from such transudation of fluid into it could not rise above that of the congested veins, and could therefore not compress the central vein.

According to Schmidt-Rimpler's [54] original theory, the raised intracranial pressure drives the cerebrospinal fluid into the vaginal space and thence into the lamina cribrosa, where it produces a compression of the nerve-fibres, a papillary œdema, and a secondary venous congestion. Manz [39] modified this view: he excluded penetration of fluid into the lamina, but assumed a direct compression of the vessels in the nerve at their entry into the lamina cribrosa by the increased sheath pressure to which they are subjected.

The main objection to these hypotheses is that no evidence of compression of the vein in the axis of the nerve has been satisfactorily demonstrated; it was certainly not present in our cases, on the contrary the vein was usually congested and engorged (fig. 10). Further, if the increased sheath pressure compress the vein, it is more likely to do so in its unsupported part as it crosses the sheath, than where it is supported by the surrounding nerve. The passage of fluid from the sheath, as Schmidt-Rimpler originally suggested, is very improbable, as the tissue tension must rise parallel with that of the veins, which must always, if circulation continue, exceed that of the compressing fluid.

Schieck [53] in a recent monograph advances the view that the increased sheath pressure obstructs the lymph drainage along the axial strand of the central vessels, from the papilla and vitreous and may even drive the sheath fluid into the lymph spaces of the nerve. Thus œdema and swelling of the disc are produced, and by pressure on the central vessels a secondary venous engorgement. This hypothesis loses sight of the fact that the intravenous pressure must exceed the sheath pressure, and, consequently, a pressure transmitted from this to the lymph in the tissues cannot compress the vein. Further, if there were the free lymph communication which he assumes between the vitreous and the papilla, the œdematous fluid in the latter would escape into the vitreous, and so drain away through the anterior chamber, without swelling of the disc necessarily resulting.

Saenger's [52] views have not yet been published in detail, but as far

as we can gather from a short abstract of his recent address, he believes that the sheath is first distended by cerebrospinal fluid, but as the intracranial pressure rises the optic nerve is compressed, and the communication of its sheath with the intracranial cavity is cut off by the pressure of the frontal lobe from above and the temporal lobe from the outer side on the dural fold that surrounds the nerve at its entry into the canal. In this way the flow of lymph in the nerve is obstructed and a papilloedema results. In the circumstances it would be unfair to criticize this hypothesis in detail, but we must again draw attention to the fact that tumours which lie in the neighbourhood of one optic foramen or compress one optic nerve from above may arrest or prevent the development of papilloedema in the corresponding eye, and when the tumour invades this neighbourhood after neuritis has appeared it may cause a rapid subsidence of the swelling and induce a pressure atrophy. Further, it is a well-ascertained clinical fact that even moderate pressure on the nerve interferes first with the function of the macular fibres, and thus gives rise to a central scotoma, which is exceedingly rare in papilloedema.

Behr [4] has adopted a similar explanation from his study of a case of oxycephaly, but he assumes, in addition to compression of the nerve in its foramen that the lymph stasis that results from this compresses the vein in the nerve and thus produces the venous congestion and engorgement in the fundus. But as lymph is secreted only at capillary or venous pressure its tension can never rise sufficiently high in the tissues to interfere with the venous circulation.

Though it is impossible to accept compression of the nerve in its foramen, as assumed by Saenger and Behr, as the cause of papilloedema, we think this may be an important factor in cutting short the course of a papilloedema (as it must, if our hypothesis be correct) and in producing a secondary atrophy which may be indistinguishable ophthalmoscopically from a primary atrophy.

According to Deyl's [12] hypothesis the site of venous obstruction is in the dural sheath. The displacement of this by distension of the space produces an acute bending and compression of the vein as it enters the dura and so obstructs the venous outflow. But, like Elschnig [16] and others, we failed to find any anatomical evidence of this compression of the vein in the dura or of the engorgement he describes in the portion that crosses the space. Dupuy-Dutemps [13] originally supported Deyl, but in his later paper [14] he regards it as more probable that the compression takes place in the space or under the pia mater.

Henderson [24], in his recent book on "Glaucoma," suggested on *a priori* grounds that papillœdema is due to the difference between the pathologically raised intravenous tension and the normal intra-ocular tension.

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PROGRESSIVE SPINAL MUSCULAR ATROPHY OF INFANTS AND YOUNG CHILDREN.

BY FREDERICK E. BATTEN, M.D., F.R.C.P.

INTRODUCTION.

THE occurrence of progressive paralysis and muscular atrophy due to a lesion of the lower motor neuron is a condition of some rarity both in infants and young children. During the past ten years I have seen some eight cases which may be placed under such a heading. Some of these have been under my own care, others under the care of my colleagues, but I have made the pathological examination in all cases in which an autopsy has been obtainable. Some of these cases have already been published. It is from a consideration of these cases that I propose to deal with the somewhat difficult problem of progressive spinal muscular atrophy of infants and young children. It will be well in the first place to mention certain classes of cases, which though they may show progressive muscular atrophy dependent or independent of spinal disease, it is not intended to deal with in this paper. Into this category are placed: (1) The primary muscular atrophies (myopathies) and with these I include the condition known as "myatonia congenita"; (2) the effects of acute poliomyelitis; (3) spinal or spinal root injury; (4) congenital defects of the cord; (5) the peroneal type of muscular atrophy (Charcot-Marie-Tooth); (6) von Recklinghausen's disease; (7) the effects of spinal caries and spinal growth.

The eight cases on which this paper is based may be arranged in three classes; each class will be dealt with in a separate chapter. A short statement of the clinical and pathological features of the cases belonging to each class will be found at the beginning of the chapter; but for a full clinical report and details of pathological examination reference should be made to the appendix for those cases not already published, and to the article referred to for those which have been published.

Of the eight cases *six* belong to the first class, *one* to the second class, and *one* to the third class. The characters of these three classes may be stated as follows:—

(1) A type of case in which progressive muscular weakness occurs during the first weeks or months of life, gradually progresses, and terminates in death after a variable period of weeks, months, or years. Sometimes more than one member of the family may be affected. Atrophy of the cells of the anterior horn is the constant pathological change found in such cases, but it may be associated with other changes in the central nervous system (Werdnig-Hoffmann type).

(2) A type of case in which progressive muscular weakness and atrophy begins somewhat later in life, after the child has already walked, and slowly progresses till death occurs from respiratory failure or pneumonia. The pathological changes found in such cases is a degeneration of the lower motor and sensory neurons resembling those occurring in a "toxic neuritis."

(3) A type of case in which progressive muscular weakness and atrophy begins in later life after the child has already walked, slowly progresses, and is attended by very marked degeneration of the spinal cord, not limited to any one group of cells or tracts (a "myelitis").

Chapter I.—Werdnig-Hoffmann Type.

The cases which belong to this type are six in number, and the following is a short abstract of the clinical features and pathological changes in those cases in which a *post-mortem* was obtained:—

Case 1.—Charles H., aged 4 weeks. First child of healthy parents; no miscarriages. Said by the mother to be healthy at birth. Took breast well for fourteen days; then fed on goat's milk. Wasting and weakness of the limbs noted when 14 days old; got tired when sucking. The child never cried well.

On admission to hospital, small child, 5½ lb., feeble cry. A complete flaccid paralysis of arms and legs, with slight movements of fingers and toes, neck muscles flaccid. Sucks well, no regurgitation; deep reflexes absent, sensation apparently normal, no reaction obtained in muscles by strong faradic current. Death after three days.

Post-mortem.—Nothing abnormal to naked eye in visceral or nervous system. No evidence of birth injury. Microscopical examination: Marked degeneration of anterior nerve-roots throughout the cord; some chromatolysis of anterior horn cells; no evidence of muscular degeneration. (See figs. 1, 2, 3, 4, 5, 6.) (See Appendix.)

Case 2.—William G., aged 5 weeks. The eighth of eight children, three of whom have died of a similar complaint within the first few months of life. The labour was difficult. On admission to hospital the child was well nourished, looked healthy, and took food well. There was complete flaccid paralysis of all four limbs, except for slight movements of the fingers. There

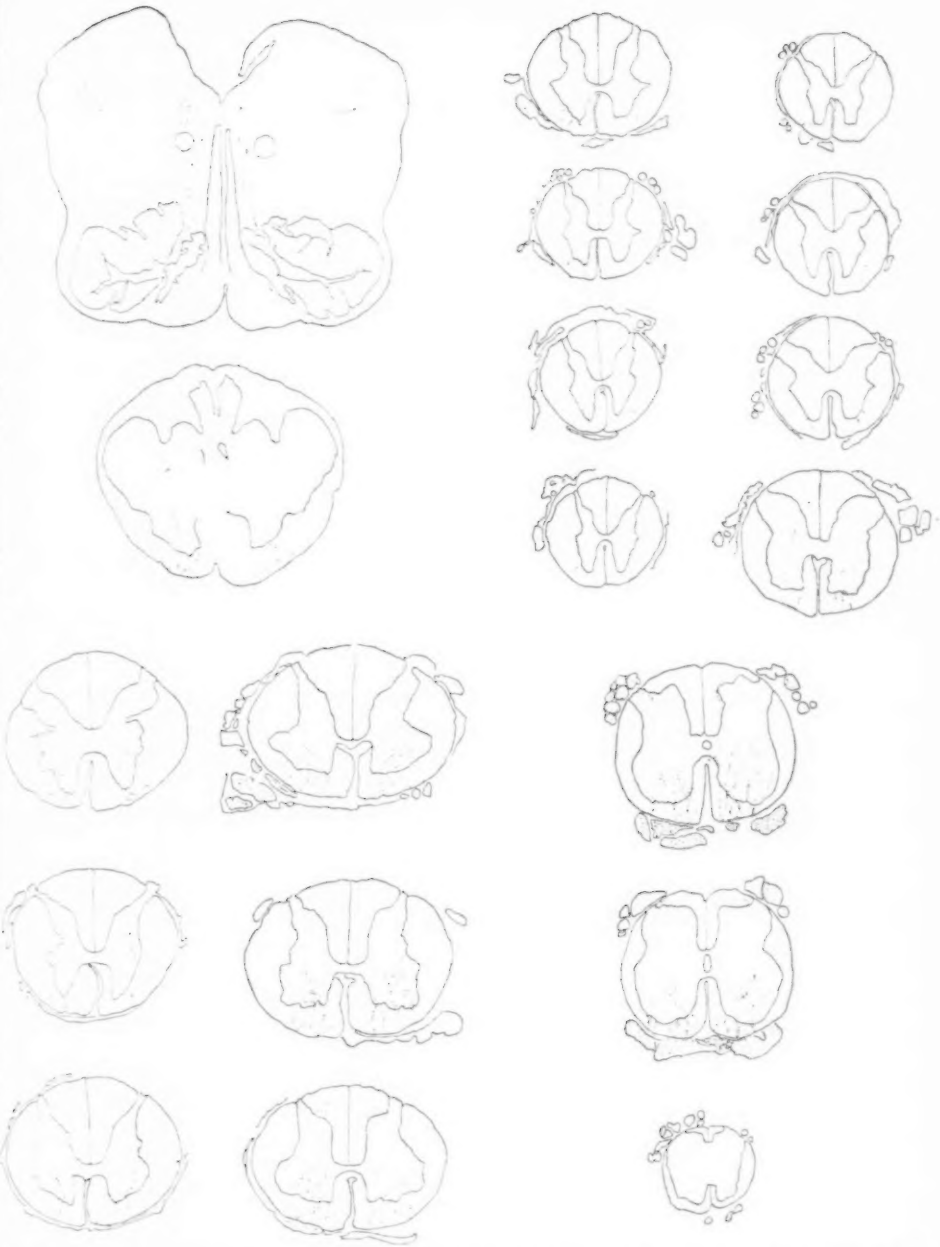

FIG. 1.—Series of section through the spinal cord, from the Case 1, Charles H., stained by the Marchi method, showing the degeneration of the anterior root.
The stress of the disease is seen to fall on the lumbar and the cervical region of the spinal cord, but some degeneration is present throughout the whole length of the cord and medulla.

was complete paralysis of the trunk muscles and intercostals, but the diaphragm acted well. All the deep reflexes were absent: there was analgesia below the second rib. The child died when 8 weeks old of broncho-pneumonia.

Post-mortem.—Nothing abnormal on macroscopical examination: but on microscopical examination widespread atrophy of the cells of the anterior horn, and degeneration of the fibres of the posterior column. (See figs. 7 and 8.) (See BRAIN, 1902, XXV, 85.)

Case 3.—Edward T., aged 4 months. Fourth of four children, one of whom was said to have died of a similar complaint. Easy labour. General helplessness noticed one week after birth: gradually increased. On admission, flaccid paralysis of arms and legs, absence of deep reflexes, paralysis of intercostals. Death. No *post-mortem*. (See Appendix.)

Case 4.—Percy B., aged 6 months. Fourth of four children. Full term: normal labour. Healthy at birth. Gradual onset of weakness first noticed in the arms when 4 months old. Well nourished, intelligent child. Flaccid paralysis of arms, legs, trunk, neck. Paralysis of intercostals. Absent reflexes. Sensation apparently normal. Death. No *post-mortem*. (See Appendix.)

Case 5.—Henry C., aged 8 months. Third of three children, others healthy. Breast-fed. Normal labour. Always weak: never able to sit up or hold its head up. Weakness has increased.

There was flaccid paralysis of both arms, and both legs. Weakness of back muscles with lateral curvature of the spine. Knee-jerks only obtainable with difficulty.

Death after four days in hospital.

Post-mortem.—Nothing abnormal on macroscopical examination. On microscopical examination some degeneration of the anterior roots and some chromatolysis and atrophy of the cells of the anterior horn. (See Appendix.)

Case 6.—Ronald A., aged 3½ years, one of twins. Never learnt to sit up. Learnt to talk early. When 15 months old could not move his legs, but could move the arms.

When first seen in June, 1910, he was quite intelligent, had flaccid paralysis of both legs, was quite unable to sit up or maintain a sitting position: he could, however, hold up his head. Sensation was perfect. The knee-jerks were absent. The intercostals paralysed. He died from broncho-pneumonia in September, 1910.

Post-mortem.—Broncho-pneumonia. Microscopical examination showed smallness of anterior nerve-roots of the spinal cord, and marked atrophy of the cells of the anterior horns. No Marchi degeneration. No vascular change. (See figs. 9 and 10.) (See Appendix.)

CLINICAL FEATURES OF CLASS I.

An infant born at full term and apparently normal at birth begins in the first few weeks of life to show weakness of the trunk and limbs. The infant appears of normal intelligence. The weakness steadily

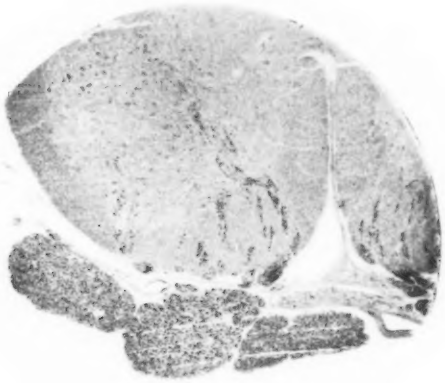

FIG. 2.—Photograph of the anterior region of the sacral cord from Case 1. Charles H., showing the degeneration of the anterior nerve-roots in their intramedullary course. Stained by the Marchi method.

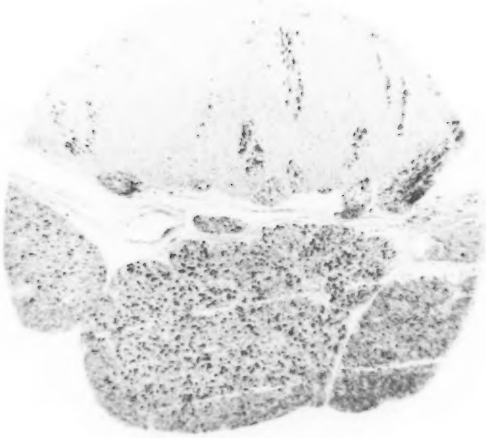

FIG. 3.—Photograph of anterior roots showing degeneration of the anterior roots in their extramedullary course. Stained by the Marchi method.

progresses, so that there is a complete flaccid paralysis of both arms and legs, and only a little movement is preserved in the fingers and toes. The intercostal muscles become paralysed and the child dies from some intercurrent disease, generally of broncho-pneumonia. Several members of a family may in succession be affected, as in the Case 2, where four children out of a family of eight were thus affected. In Case 3, another member of the family is said to have died from the same disease.

The clinical picture which these infants present is very striking: The infant lies in bed, happy and contented, taking his food well, but completely unable to move either arms or legs, the limbs being perfectly flaccid. The disease tends to affect the proximal muscles before the

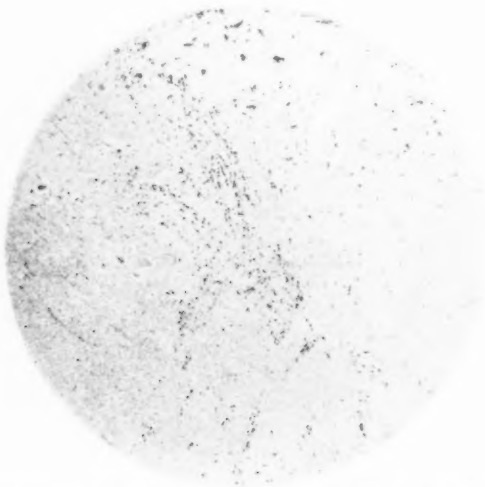

FIG. 1.—Photograph of grey matter, showing degeneration of fine fibres arising from cells of anterior horns. Stained by the Marchi method.

distal, so that all movements of the fingers and toes are still possible after power has been lost in the shoulders and hips. If an attempt is made to lift up the child the extreme flaccidity of the trunk muscles is easily recognized. The actual wasting of muscles in some cases is not obvious, for it is covered up by the subcutaneous fat. The child will, as a rule, rapidly respond by crying when pricked by a pin, and as far as can be judged, sensation is perfect. All the tendon reflexes are either

absent or greatly diminished. In those cases in which the electrical reactions have been examined the absence or great diminution of excitability to the faradic current is a most striking feature. The duration of life in most of these cases is limited by months, but in one case of the present series the duration of life was considerably longer, viz., three and a half years.

Pathological Features of Class 1.

The clinical features of the disease are fairly constant. The pathological features differ somewhat. These differences may depend upon the length of time the disease exists before a fatal issue ensues; for that issue, although dependent in part on the progress of the disease, and especially on the paralysis of the intercostal muscles, yet it is often accelerated by the occurrence of broncho-pneumonia.

In four of the six cases belonging to this class a pathological examination was made, viz., Cases 1, 2, 5, 6.

In Case 1 there is the most marked degeneration of the medullary sheath of the fibres of the anterior roots of the spinal cord from their origin in the cells of the anterior horns, in their intramedullary course through the cord, and in their extramedullary course. (Figs. 1, 2, 3, 4.) This degeneration is most strikingly shown by the Marchi method. The peripheral nerves show but little change. The cells of the anterior horns show but little change, when considered in relation to the marked change in the fibres. Some few cells undoubtedly show chromatolysis (figs. 5 and 6), but only a few compared to the numbers of fibres which are affected. (Compare figs. 1, 2, 3, 4, 5, 6.)

The muscles in Case 1 do not show any marked change, the muscle-fibres being in the condition seen in a late fœtal or infantile life.

The changes met with in Case 2 are somewhat different. In this case there is a marked atrophy of the cells of the anterior horn throughout the cord (figs. 7 and 8), without the striking degeneration of the anterior roots as shown by the Marchi method. There is some degeneration of the posterior column of the spinal cord. The muscle shows a curious mixture of atrophy and hypertrophy of muscle-fibre, but no fibrosis.

The changes met with in Case 5 are similar to those in the two former cases, but differ in the following respects, viz., that the Marchi degeneration is less marked than in Case 1, and more marked than in Case 2, while the chromatolysis is more marked than in Case 1 and less marked than in Case 2.

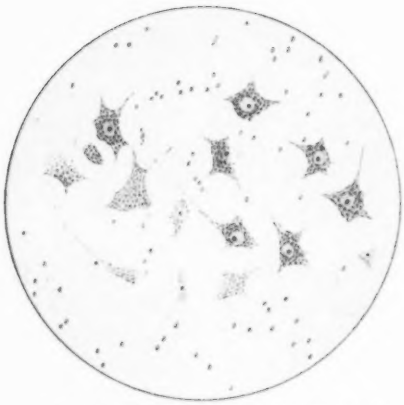

FIG. 5.—Cells of the anterior horns of cervical region, stained by the Nissl method, from Case 1, Charles H. Most of the cells appear normal, some, however, show slight chromatolysis.

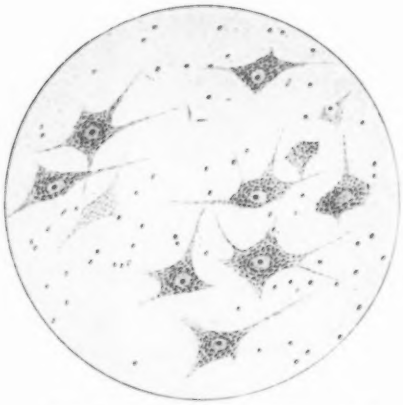

FIG. 6.—Cells of the anterior horns of the lumbar region, stained by the Nissl method, from Case 1, Charles H. The cells as a whole appear strikingly normal in appearance, considering the marked change seen by the Marchi method; some, however, show slight chromatolysis.

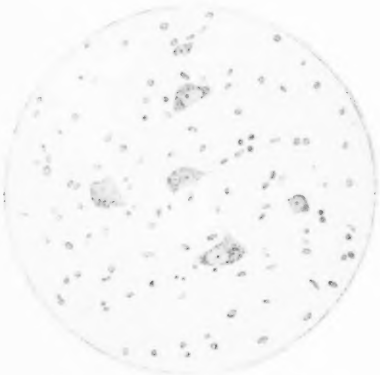

FIG. 7.—Cells from the anterior horns of the cervical region, stained by the Nissl method, from Case 2, William G., showing marked atrophy. Compare them with the normal-sized cells of fig. 5. *Drawn under same magnification, 170 diameters.*

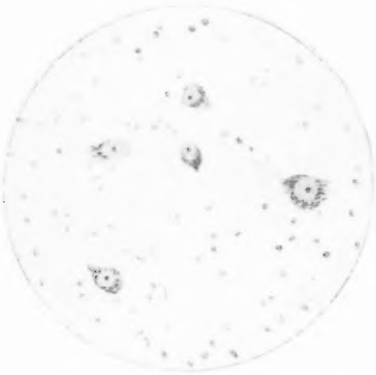

FIG. 8.—Cells from the anterior horns of lumbar region from Case 2, showing same condition.

The changes met with in Case 6 are similar to those seen in Cases 2 and 5, viz., the marked atrophy of the cells of the anterior horns, and of the anterior roots, only a few normal cells persisting. (Figs. 9 and 10.)

If the pathological findings in these four cases are carefully considered together, may not the differences be explained partly by the intensity of the poison, and partly by the duration of the disease? In Case 1 the appearance is very similar to that met with in diphtheritic paralysis, the most marked changes being visible in the medullated sheath of the nerve, whilst the cells exhibit but little chromatolysis. At a later stage the products of degeneration shown by the Marchi method become absorbed, whilst the chromatolysis and atrophy of the cells as

FIG. 9.—Cells from the anterior horns of the cervical region, stained by Nissl method, from Case 6, Ronald A., showing marked atrophy of cells, two normal cells alone remaining.

FIG. 10.—Cells from lumbar region of Case 6, showing similar changes. *Magnification* 170 *diameters*.

shown by the Nissl method become more marked. Such a condition is well exemplified in Case 5, where there is a condition both of chromatolysis and atrophy of the cells, with some degeneration of the myelin sheath of the fibres, an appearance compatible with a more chronic course, dependent on a lesser dose of the toxin. The longer clinical history of this case corresponds with such a result.

In Case 6, a case of three years' duration, the cells and roots have undergone atrophy, and the pathological picture represents the later stages of the disease.

The question as to the nature of the toxin to which these changes

are due may be raised, but on that point there is yet no evidence. Certain poisons are known to act especially on the lower motor neurons, and as an instance of such, diphtheria, lead and arsenic may be quoted.

The changes found in Case No. 1 resemble closely those found in diphtheritic paralysis, and it might be suggested that the mother had diphtheria before the birth of the child, and the resulting degeneration was due to that poison. Lead and arsenic might similarly be thought of, but the only object of such hypotheses is that in investigating future cases, examination might be made for these poisons. On the other hand, the occurrence of the disease in families, although not absolutely excluding the toxin theory, yet renders such a view improbable, and would seem to point to the condition being due to what Sir William Gowers has termed an "abiotrophy," that is, a "degeneration dependent on a defective vital endurance."

Recently Catola has examined the nervous system of infants born of parents suffering from various diseases. The changes which he figures and describes in the cells of the anterior horns and in the anterior roots in the child of an eclamptic mother and in that of a syphilitic mother are strikingly similar to those described in Case 1 of my series.

Chapter II.—Toxic Neuritis.

Abstract of Case.

Case 7.—Hetty M., aged 3. Weakness of limbs first noticed when 3 years old; the weakness gradually progressed, but there were considerable remissions during which the child improved. Deep reflexes became abolished. Muscles of trunk, intercostals and diaphragm became involved. Death from bronchopneumonia fourteen months after onset.

Post-mortem.—No macroscopic change in nervous system. On microscopical examination chromatolysis of the cells of the anterior horns and degeneration of the peripheral nerves. Fatty degeneration of muscles. (Figs. 10 and 11.)

Clinical Features of Class 2.

The case which is placed in this class is one which was under the care of my colleague Dr. Voelcker, and was shown by him at the Medical Society, November, 1908, and February, 1909. I saw the child on various occasions. One of the most striking features of the case was, that although the disease was slowly progressive, yet there were periods

during which improvement took place. The disease ran its course in a period of fourteen months.

The clinical features of this class as based on this case are as follows :—

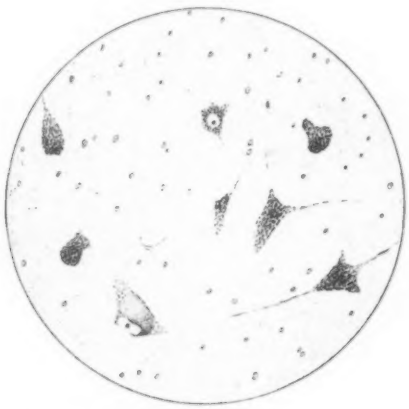

FIG. 11.—Cell from anterior horn of the cervical region from Case 7. Hetty M., showing marked chromatolytic changes. Stained by Nissl method. Magnified 170 diameters.

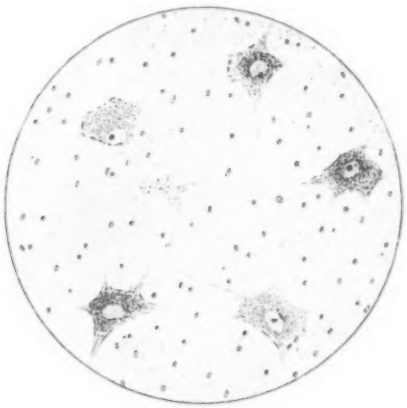

FIG. 12.—Cells from anterior horn of lumbar region, from Case 7. Hetty M., showing marked chromatolytic changes similar to those in the cervical region. Stained by Nissl method. Magnified 170 diameters.

An apparently healthy and intelligent child, who had made normal progress, without any obvious cause was noticed one morning to be

unable to walk properly and to fall after taking a few steps. This weakness gradually progressed, so that the child became unable to walk and unable to feed herself. There was incontinence of urine and fæces for a time. There was a transient weakness of the muscles of the face. All the deep reflexes became abolished. The muscles showed the reaction of degeneration. The respiratory muscles became affected. Sensation was unaffected, and there was no pain.

Some improvement took place for a few months, then the disease steadily advanced and the child died some fourteen months after the first symptom.

Pathological Features of Class 2.

The brain and spinal cord to the naked eye appears quite normal, and on microscopical examination could no change be shown by the Weigert-Pal method. Some slight degeneration is seen by the Marchi method, both in the white matter of the cord and in the anterior and posterior roots. Some of the cells of the anterior horn, both in the cervical, dorsal and lumbar region show chromatolysis, others have already undergone atrophy. (Figs. 11 and 12.)

The peripheral nerves show a considerable amount of degeneration by the Marchi method. The changes appear to be more marked in the peripheral nerves than in the central nervous system.

The muscles and fibres of the diaphragm show a marked fatty degeneration by the Marchi method.

The changes found are probably the result of some toxin affecting the lower neurons ("toxic neuritis").

This case has been classed as a "toxic neuritis," partly on clinical grounds, partly on pathological grounds. The clinical history of the case is distinct from that of the cases which form Class 1. The onset of the disease, the irregular course, the reaction of degeneration, the affections of the diaphragm, are all symptoms to which, if taken singly, no special value in the differential diagnosis could be attached, but if taken together suggest a poison acting diffusely in the lower neurons, rather than a poison which is acting primarily on the cells of the anterior horn.

On pathological grounds the extensive degeneration of the peripheral nerves as compared to the slighter changes in the cells of the anterior horns, together with the character of those changes, seem to me to be points in favour of regarding this case as one belonging to the class of "toxic neuritis."

It is admittedly one of the most difficult problems in neurology to

differentiate between cases of "toxic neuritis" and those due to degeneration of the cells of the anterior horn.

On clinical grounds there is no doubt that the distinction is useful; on pathological grounds it seems to me doubtful if the distinction can be drawn between affections of various portions of the lower motor neuron, but for the present I would classify those cases which show rather diffuse changes in the peripheral nerves, and but little change in the anterior horn cells or anterior roots, as "toxic neuritis," and those cases which show marked changes in the anterior horn cells and anterior roots, and but little or scattered degeneration in the peripheral neurons, as "spinal atrophies."

The question as to the advisability of including such a case in a series of cases described as progressive spinal muscular atrophy might be raised. Few, I think, will be disposed to press this objection against the obvious advantages of considering together cases which have a marked clinical similarity.

Chapter III.—Chronic Myelitis.

Abstract of Case.

Case 8.—Matilda L., aged 11. Twelve months' weakness of hands, four months' weakness of legs. Gradual increase of weakness and muscular atrophy. Reaction of degeneration in some muscles. Sudden death from respiratory failure eighteen months after onset of illness.

Post-mortem.—Extensive myelitis of both grey and white matter of the spinal cord, giving rise to atrophy of the cells of the anterior horns. (Brain, 1903, xxvi, p. 473.)

Clinical Features of Class 3.

The case on which the third class is described is one which was published in Brain, 1903, by Dr. Morley Fletcher and myself. It is in its clinical and pathological manifestation entirely distinct from the other two groups, and yet it possesses the characteristic feature, viz., progressive muscular atrophy of spinal origin.

The clinical features are given in the following short abstract :—

A girl, aged 11. Twelve months' weakness of hands; seven months unable to button clothes; four months' weakness of legs. Two months ago adenoids removed and much worse since that operation. Fourteen days' pain in back and increased difficulty in swallowing. Intelligent, deaf, some atrophy of tongue, palate moves well on phonation, weakness

of neck, respiration thoracic, upper intercostals only in use. Claw-hand, wrist-drop, weakness of upper arm and shoulder muscles. Can walk but feebly; knee-jerks brisk, plantars flexor. Sensation natural to all forms. Electrical reaction shows R.D. in some muscles, in others only diminution of excitability.

Sudden death from respiratory failure six months later.

Pathological Features of Class 3.

There is extensive destruction and atrophy of the cells of the anterior horn from the upper cervical to the lower thoracic segments, these changes being most marked at the level of the sixth thoracic segment; the cells of Clarke's column being also affected. There is extensive degeneration of the whole of the ventral region of the cord in the thoracic segments, the lesion being most marked at the level of the sixth thoracic segment, and diminishing in extent both towards the medulla and caudally. There is extensive degeneration of the direct cerebellar tracts, both dorsal and ventral, beginning in the lower thoracic segments and extending up to their respective termination in the cerebellum. The degeneration affects both grey and white matters alike.

There is a marked increase of the connective tissue in the ventral portion of the cord. The walls of the vessels show no change. The cords shows show both recent and old degeneration. (Brain, 1903, xxvi, 473.)

This case must be regarded as a chronic form of diffuse myelitis, secondary to some vascular changes and toxic blood state. The origin and cause of the myelitis and of the peculiar distribution is unexplained.

Chapter IV.—Diagnosis.

The differential diagnosis in the first class of cases above described is one of the greatest difficulties. A child who at the *time of birth* has a complete flaccid paralysis of all four extremities is probably the subject of a spinal hæmorrhage, due to traumatism at birth. The child who during the first few weeks or months of life *develops* a flaccid paralysis of all four extremities is probably the subject of a spinal atrophy; but the difficulty of differentiating these two conditions is well shown in the two cases recorded by Dr. Beevor. Two children, when a few weeks old, exhibited the same clinical picture, viz., that of a complete flaccid

paralysis, and yet on pathological examination it was found that in the one case the condition was due to spinal hæmorrhage, in the other to an atrophy of the anterior horn cells. In children rather more advanced in age other questions came up for consideration, and one of the most difficult is the distinction of a primary spinal condition from a primary muscular condition or myopathy.

The forms of myopathy which occur in young children become year by year more generally recognized. The "simple atrophic" type of Erb and the condition known under the name "myatonia congenita" may easily be mistaken for the Werdnig-Hoffmann paralysis. Myatonia congenita is a disease of early childhood, characterized by an extreme degree of loss of tone and feebleness in all the muscles of the body. The condition is stated to improve as the child advances in age.

A child with this disease can, as a rule, perform all movements in a feeble manner, and there is not the marked degree of flaccid *paralysis* seen in the case of spinal atrophy. Although hypotonia is present in cases of spinal atrophy, yet it is not so marked as in cases of myatonia congenita. Again, the intercostal muscles are commonly paralysed in the spinal atrophy of infants, whereas in myatonia they are less affected.

Shortly, it may be said that in spinal atrophy the paralysis is more marked and the hypotonia less marked than in cases of myatonia congenita.

The difficulty of diagnosis is well exemplified by the three cases in one family described by Finkelnburg. These would, on clinical grounds alone, be assigned to the Werdnig-Hoffmann group, and yet on pathological examination he has shown that they belong to the myopathic group—there being no change in the spinal cord, and changes in the muscles typical of myopathy.

Spinal caries may, under certain circumstances, rather closely simulate this disease, especially when the tuberculous process has spread in through the membranes and invaded the spinal cord. Cases of widespread poliomyelitis occurring during infant life may clinically resemble Werdnig-Hoffmann paralysis, but the paralysis and atrophy of muscles is rarely symmetrical, and groups of muscles tend to be picked out, leaving others unaffected.

In the second and third class the diagnosis is no more easy than in the first group, and even with the pathological knowledge obtained from the examination of these cases, it would be most difficult to assert in cases presenting similar symptoms what was the cause of the widespread progressive muscular atrophy.

Chapter V.—Literature.

Since the year 1898 there are only some five cases of the disease recorded, in which there has been a pathological examination. These are the cases recorded, one by Hoffmann, one by Beevor, two by von Ritter, and one by Armand-Delille and Boudet. Previous to that date there are the well-known cases of Werdnig and Hoffmann on which the clinical features and pathology of the disease are founded, to which may be added the case recorded by Thomson and Bruce, *i.e.*, ten cases, to these may be added the three cases in this paper, making thirteen cases in all.

Of cases without autopsy there are those recorded by Senator, Sevestre, Bruns, Wimmer, Haushalter, Lange. Some of these, and notably those of Bruns, Senator, Haushalter, and Lange, and the second case of Wimmers, should almost certainly be classified as myopathies and not with the Werdnig-Hoffmann group. The earlier cases of Werdnig and Hoffmann have already been reviewed in Brain, 1897. The later case of Hoffmann and those of Beevor, von Ritter, Armand-Delille and Boudet will be considered.

Hoffmann in 1900 recorded the result of the autopsy on the child Margarethe G., the details of whose case had already been published in 1897. The paralysis slowly progressed, only feeble movements of the hands and feet remaining till the end. The face, tongue, muscles of deglutition, remained unaffected. The higher senses were normal, and there was no affection of the bladder or rectum. Sensation remained intact. The child died when 5 years old of pneumonia. On examination of the spinal cord there was found to be atrophy of the intra- and extra-medullary portions of the anterior roots, degeneration and wasting of the multipolar ganglion cells, and degeneration of the peripheral nerves. The pyramidal tracts showed no change. There was wasting of the muscle-fibres with fatty degeneration and interstitial fat.

Beevor's case, published in 1902, is recorded in the Appendix, and is one of those included in the substance of the paper. Shortly, the leading features are as follows: An infant, the eighth of a family of eight, four of whom had been similarly affected, had flaccid paralysis of all four limbs. The child died at 2 months old, and extensive atrophy of the cells of the anterior horns was found.

Von Ritter, in 1904, described two cases. The first, a female child, 15 months old at the time of death, the only child of healthy parents, born in normal labour, and suckled till 10 months old. When

5 months old it was noticed that the child moved its legs but little, and she seemed to get weaker in the upper extremities. The child was fat, not rickety, and had a flaccid paralysis of all its limbs. The face, mental condition, sight, and hearing were quite normal. On examination, the spinal cord showed marked atrophy of the cells of the anterior horns and atrophy of the muscle-fibres, with fatty degeneration. The second case, a female child, the second of two children, the first being quite healthy. The birth was normal. During the first year of life the parents noticed nothing amiss. In the second year of life the child gradually began to develop weakness in the lower extremities, and she had, by the end of the second year, complete loss of power in the legs, and had paresis of the arms. There was marked wasting of the buttocks, standing was impossible, sitting was possible, all the visceral functions were normal, the deep reflexes were abolished. The child died when 2 years old. On pathological examination, the anterior roots of the spinal cord were found to be very wasted, and very few normal ganglion cells remained. The muscles showed atrophy of the muscle-fibres and a marked lipomatosis. The cord does not seem to have been examined by the Marchi method.

Armand-Delille and Boudet, in 1908, described the case of a child, 5 months old, the first of two healthy parents. The infant had made normal movements of the new-born during the first weeks of life, but when 2 months old weakness of the limbs was noticed. The muscles of the neck were also weak, and the head flopped to the side.

On examination there was almost complete paralysis of the four limbs and muscles of the neck. There was paralysis of the intercostal muscles. The diaphragm alone carried on respiration. The thorax was deformed. Cutaneous sensation was preserved. All the deep reflexes were abolished. There was absence of response in the muscles, both to faradic and galvanic currents. The sphincters were intact. On account of the subcutaneous fat it was impossible to feel the muscles, which were paralysed and in the course of atrophy. The child died when 5 months old. On examination of the muscle, the nuclei appeared very abundant, and the muscle-fibres markedly degenerate. Some bundles were completely replaced by connective tissue, some of the muscle-fibres preserved their striation, but most were already in a stage of advanced atrophy. A perivascular and interstitial sclerosis was present. The muscle-fibres of the diaphragm were normal. In the peripheral nerves a number of the fibres had disappeared. The anterior roots were

atrophied, the posterior roots were intact. The posterior root ganglia showed no change. The white matter of the cord was normal. There was very marked atrophy of the cells of the anterior horns and of the anterior roots. The cells which were less affected showed chromatolysis. The atrophy of the cells of the anterior horn contrasts with the normal appearance of those of Clarke's column. The meninges were intact. All these cases may be accepted as examples of the disease.

The cases, without autopsy, arrange themselves in two groups—those which from their clinical symptoms may be considered as examples of the disease, and those which from their clinical symptoms, it would not seem justifiable in the absence of any pathological evidence to the contrary, to include under the Werdnig-Hoffmann group.

Group I.—Cases which, from their Clinical Symptoms, and without an Autopsy, may be considered as Examples of the Werdnig-Hoffmann Type.

In the first group may be placed the cases of Sevestre and Wimmer's first case, while in the latter group I should place those of Hausalter, Bruns, Senator, and Lange.

Sevestre showed the case of an infant 2½ months old, with complete flaccid paralysis of the body, only the muscles of the head, neck, and diaphragm remaining normal. The muscles of the extremities were atrophic, and they had lost their faradic irritability and gave an anodal contraction on galvanic stimulation. The thorax was deformed. Two other members of the family of six had had the same affection and had died when a few months old. In the discussion Hutinel said he had seen a similar condition in two children born in a breech presentation, and he attributed the condition to spinal hæmorrhage. In one case, however, in which an autopsy was obtained, no such hæmorrhage was present.

Wimmer's case is that of a boy, aged 16 months. The labour was normal, and no other members of the family were affected. A few months after birth difficulty in sucking was noticed. The infant was always very weak, could not raise the arms, but could move the fingers and hands. The child could move the toes, but not the legs or thighs. The neck muscles were weak. The child was not imbecile, had no enlargement of the head, and the movements of the face, eyes, and tongue were normal. The child was a cryptorchid. The deep reflexes were absent. The muscles showed altered electrical reactions. He compares it to Beevor's case and says that it most resembles that.

Group 2.—CASES WHICH, FROM THEIR CLINICAL SYMPTOMS, AND WITHOUT AN AUTOPSY, *SHOULD NOT*, IN THE OPINION OF THE WRITER, *BE REGARDED* AS BELONGING TO THE WERDNIG-HOFFMANN TYPE.

With regard to the second group of cases without autopsy, recorded by Haushalter, Bruns, Senator, and Lange, I am unwilling to accept any of these as cases of muscular atrophy due primarily to atrophy of the cells of the anterior horn. Haushalter, indeed, regards his cases as primarily myopathic, though described under the title "Amyotrophie primitive progressive dans l'enfance," the first being a fairly typical case of facio-scapulo humeral type, the second belonging to the simple atrophic type, and the third probably to the myatonia congenita type, though in many features this case most closely resembles the Werdnig-Hoffmann type.

Bruns records three cases from different families. In the first family two sisters had died of the same complaint. In the second family there was no other case. In the third family the two elder and one younger members were healthy. Bruns counts these as five cases, and added to the nineteen cases already published by Hoffmann, and the two cases by Werdnig, and one by Bruce, says that there are now twenty-eight recorded cases of the disease.

The first case is that of a girl, I. R., aged 10, the fourth of four children. The family history was as follows: The first child, a boy, stood and walked at 9 months. Paralysis then occurred and he died when 4 years old. The second, a girl, died from inflammation of the lungs when 3 years old. The third, a boy, normal at birth, developed well till 9 months old, began to sit up, but could not stand, the hands were unsteady. When $2\frac{1}{2}$ years old he was examined. The child could just sit up, but easily fell backward. The legs could not be bent at the hips, the weakness of the quadriceps extensor was very marked. There was loss of faradic irritability in the muscles, and a very weak reaction to galvanism. The weakness gradually extended and the child died when 3 years old. There was no *post-mortem*.

The girl, I. R., developed fairly well in the first two years of life. She nearly walked at $1\frac{1}{4}$ years, after which no progress was made. She frequently fell, and her gait became progressively worse. Weakness of the arms came on at a later date. When seen in 1894 there was very marked curving of the spine, wasting and feebleness of the arms, a weakness of the legs. The paralysis was of a flaccid character. The deep reflexes were absent. The lower arm and hands were less affected than the shoulder muscles, and the toes less affected than the upper portion of the leg. Fibrillary tremors were present. There was loss of electrical excitability, but no distinct reaction of degeneration. Intelligence, sensation and sphincters were normal. In 1896 the weakness had

increased and she had difficulty in holding up the head. In 1898 there was still more weakness, atrophy of the shoulder girdle and the thighs, and more wasting of the calf muscles. In 1900 she died, when 16 years old. There was no autopsy.

The second case, E. F., aged 11. Nothing is known of the family history. She had general weakness of the shoulders and hips, standing was impossible, there was a marked kyphosis, fibrillary tremor in the shoulder muscles, diminished electrical reaction, absence of the deep reflexes. She remained in this condition.

The third case, A. N., boy, aged 3: two older brothers, aged respectively 7 and 5, are healthy, as is also the sister, aged 8 months. This child walked and talked at 1 year and 3 months. When 2 years old the mother noticed gradually increasing weakness. The child lost the power of walking, developed a tremor of the hands and weakness of the back. The legs showed the greatest amount of weakness. The face, eye, muscles of the tongue were unaffected. There was fibrillary tremor of the muscles of both hands. Kyphosis was present in the lumbar region and the deep reflexes were absent.

Bruns, in considering these cases, says they are undoubted cases of Werdnig-Hoffmann's disease. He notes the difference in age between his cases and those of Werdnig and Hoffmann, but he says that they cannot be mistaken for any progessive form of muscular dystrophy. He suggests that Charcot-Marie-Tooth or peroneal is the type which most resembles these cases, but the atrophy in these begins in the peripheral portion of the limbs and extends upwards.

I should not be prepared to agree with this statement, for the cases rather closely resemble some of the forms of dystrophy, which begin in the proximal muscle, and a very similar case with curvature of the spine has been figured by Jendrassik (see Case 10, *Deutsche Zeitschr. f. Nervenheilk.*, 1902, Bd. xxii, S. 444). Without a pathological examination Bruns is hardly justified in placing in the Werdnig-Hoffmann group a type of case which differs so markedly in course and clinical features from that group.

Senator describes two cases, a brother and sister, under the title "Zur Kenntniss der familiarem progressive Muskelatrophie in Kindesalter."

The first case is that of a boy, aged 8, healthy at birth. He walked at 11 months. When 2 years old he often fell. Walking and standing became more difficult, so that when 3 years he had nearly always to be carried. He learnt to write, but when between 6 and 7 he lost this power, owing to the shaking of his hands. His memory also began to fail. There was atrophy of the shoulder and upper arm muscles, atrophy of the back muscles, moderate lordosis and the muscles showed fibrillary tremors. The knee-jerks were

absent, sensation was natural. There was altered electrical excitability. Six months later the atrophy of the buttocks and shoulders had made further progress. The gait was unaltered. He was neither better nor worse.

The second case, G. S., a girl, aged 5½, walked at 10 months. When 18 months old she had a fit. When 2 years old she became unsteady on her legs, like her brother, and at the same time there was tremor of the hands. She walked with a wide base, was shaky, had marked lordosis and a lateral curvature with the convexity to the right. There was wasting of the back muscles and to a lesser degree of the upper arm and pectoral muscles. The buttock muscles were flabby, but the lower legs appeared well developed. Fibrillary tremor was present in some muscles. There was diminished excitability in the muscles.

Senator, in considering the differential diagnosis of these cases, questions whether they belong to the neuropathic form of Werdnig and Hoffmann, or to Erbs' myopathic form of simple atrophy. He says that Heubner, Schulz and Preisz have shown changes in the nervous system in some cases of myopathy. He thinks these two cases are probably spinal in origin.

Lange describes two cases, a brother and sister, aged 11 and 6 respectively, the first and fourth children of a family of six. The second child was said to have died of a similar complaint when 3 years old.

The first case, a boy, did well for the first nine months of life, then he began to lose power in the limbs, lost the power of sitting up, and also the power in the neck muscles. When 3 he developed double cataract.

When 11 years old he was unable to stand, there was marked wasting of the proximal muscles of the limbs. The shoulders were loose. The knee-jerks were absent.

The second child, sister of the above, aged 6, was quite well till 9 months. Then the legs began to waste. She never learnt to walk. When 3 years old she, like her brother, developed cataract. She could only sit when propped up.

Lange is inclined to attribute these cases to the Werdnig-Hoffmann group, but he says it is impossible to separate such cases from the myopathies without a pathological examination.

In conclusion, as belonging to the Werdnig-Hoffmann group one would accept in addition to the case of Hoffmann, published in 1900, Beevor's case, von Ritter's two cases, Armand-Delille and Boudet's case, all with the pathological examination, and also Sevestre's and Wimmer's first case without a pathological examination. I should not, however, be prepared to accept as belonging to this group the cases of Bruns, Senator and Lange without a pathological examination.

The following list of thirteen cases comprises all those in which the

diagnosis has been confirmed by autopsy, and may be accepted as belonging to the Werdnig-Hoffmann type. They have been arranged according to the age at which death occurred. The list shows the marked variation in the duration of symptoms.

Recorder	Age of onset	Sex	Age of child	Family history	Year of publication
1. Batten ..	14 days ..	M.	5 weeks ..	0	1911
2. Beevor ..	Birth	M.	2 months ..	Yes	1900
3. Armand-Delille and Boudet	2 months ..	M.	6 months ..	0	1908
4. Batten ..	Always weak ..	M.	8 months ..	0	1911
5. v. Ritter ..	5 months ..	F.	15 months ..	0	1904
6. v. Ritter ..	12 months ..	F.	2 years	0	1904
7. Hoffmann ..	7 months ..	F.	2½ years ..	Yes	1897
8. Werdnig ..	10 months ..	M.	3 years	Yes	1891
9. Batten ..	Always weak ..	M.	3½ years ..	0	1911
10. Hoffman ..	9 months ..	F.	5 years	Yes	1893
11. Hoffman ..	4 months ..	F.	5 years	Yes	1900
12. Werdnig ..	10 months ..	M.	6 years	Yes	1894
13. Bruce and Thomson	12 months ..	F.	6 years	0	1893

Summary.

The paper deals with the widespread progressive muscular atrophy of infants and young children due to a spinal lesion. The paper is based on the clinical and pathological examination of eight cases. These, on pathological grounds, are divided into three classes:—

(1) A type of case in which progressive muscular weakness occurs during the first week or month of life, gradually progresses, and terminates in death after a variable period of weeks, months, or years. Sometimes more than one member of the family may be affected. The pathological change found in these cases is a degeneration of the lower motor neurons, the character of the change depending on the time after the onset of the disease at which death takes place. The type corresponds to the cases described by Werdnig and Hoffmann.

(2) A type of case in which progressive muscular weakness and atrophy begins somewhat later in life, after the child has already walked, and slowly progresses till death occurs from respiratory failure or pneumonia. The pathological changes found in such a case resemble those found in a toxic neuritis.

(3) A type of case in which progressive muscular weakness and atrophy begin in later life, after the child has already walked, slowly progresses, and is attended by a widespread myelitis of the spinal cord.

Six of the recorded cases are assigned to the first group, one to the second, and one to the third.

The literature is then considered. Ten cases belonging to the first group are at present on record with a pathological examination; two recorded by Werdnig, three by Hoffman, two by v. Ritter, one by Bruce and Thomson, one by Beevor, and one by Armand-Delille and Boudet.

Of recorded cases assigned to the Werdnig-Hoffmann group without an autopsy, the writer is unwilling to accept those of Senator, Bruns, Lange, and the second case of Wimmer's, but would accept Wimmer's first case, and that recorded by Sevestre.

The great difficulty in the diagnosis of these cases from cases of primary myopathy is recognized, and reference is made to cases recorded by Finkelnburg, which on clinical grounds might well be assigned to primary spinal atrophy, but on pathological grounds was shown to belong to the myopathic group.

Appendix.

Case 1.—Charles H., aged 4 weeks, was seen at the Children's Hospital, Great Ormond Street, in May, 1903. The child was the first. The parents were healthy. There had been no miscarriages, the labour had been prolonged, but no instruments had been used. At birth the cord was round the child's neck, and the child was cyanosed. The child was breast-fed for the first fourteen days and seemed to thrive. It was then fed on goats' milk. Wasting and loss of power in the limbs was first noticed when the child was 14 days old, and the child gradually became feebler. The child sucked well, but seemed to get easily tired. There was no vomiting. The child had been rather constipated. On examination the child was small, wasted, weighing 5½ lb. It lay with the arms at its side and did not attempt any movement. Respiration was feeble, the pulse from 84 to 96 per minute. The child seemed to see and to take notice. The eye movements were good, it sucked well, and there was no paralysis of the tongue or palate. There was no regurgitation: it cried fairly well: there was complete flaccid paralysis of the muscles of the neck.

The arms lay quite flaccid by the side or across the abdomen, or wherever placed. The child was just able to move the fingers, the arms were thin and wasted. There was no power in the muscles of the back, and very little in the intercostal or abdominal muscles. There was almost complete flaccid palsy of all the muscles of the leg, but some slight movement remained in the toes. The knee-jerks were absent. The child certainly felt a pin-prick all over the body.

On electrical examination of the muscles no contraction could be obtained to strong faradic current in any of the muscles of the arm, trunk, or leg. The child died three days after admission to the hospital. On *post-mortem*

examination nothing abnormal could be found on naked-eye examination in the visceral or nervous system. The brain and spinal cord, the right median, the right phrenic, left sciatic nerves, and biceps muscle were preserved for examination.

The examination of the tissues was carried out by the Marchi, Nissl, Weigert-Pal, and Van Gieson methods.

Microscopical examination. — The spinal cord by the Marchi method showed at the level of a third sacral segment marked degeneration in the finer fibres of the grey matter of the anterior horns (fig. 4). These degenerate fibres arising from the cells of the anterior horn form bundles which can be seen passing through the white matter of the cord towards the peripheral, where they form, after their exit from the cord, the anterior roots. Numerous degenerate fibres can be seen in these anterior roots (figs. 2 and 3). The fibres of both anterior horns are about equally affected. The cells of the anterior horn appear for the most part normal and show no evidence of pigmentation or degeneration. It is not possible to assert that one group of cells have more degenerate fibres arising from them than another group. No degenerate fibres could be seen in the antero-lateral tracts other than those above mentioned, which were passing outwards to the anterior roots. In the posterior columns, however, a few degenerate fibres could be seen in the posterior root zone, and also in the posterior roots both within the cord and outside.

At the level of the third lumbar a similar condition was present—viz., degeneration of the fine fibres passing from the anterior horns to the anterior roots. A few degenerate fibres were also present in the posterior columns and roots.

At the level of the first lumbar the degeneration becomes less marked, but a few degenerate fibres can now be seen in the region of Clarke's column, and although they cannot be traced to the direct cerebellar tract, yet they tend in that direction, and scattered degenerate fibres can be seen in this tract. A few degenerate fibres are present also in the posterior columns and roots.

Throughout the dorsal region but little degeneration can be seen (fig. 1). There are a few degenerate fibres in the anterior horns and also in the posterior columns, but the cells of Clarke's column appear normal, and there are no degenerate fibres in that region. (Figs. 1, 2, 3, 4.)

At the level of the first and second dorsal segments degenerate fibres again become more numerous, and at the level of the sixth cervical segment marked degeneration is again present in the grey matter of the anterior horns (fig. 1.) The degeneration is more marked about the median group of cells, and least about the lateral group. In the posterior columns there are a few degenerate fibres, whilst there are practically no degenerate fibres in the antero-lateral tract. All through the cervical region there is considerable degeneration which, however, becomes less marked again in the upper cervical segments. There is a small bundle of fibres situated at the root of the posterior horn, which contains degenerate fibres: this can be traced from the seventh cervical segment upwards to the lower portion of the medulla, where it apparently leaves the cord by a lateral nerve-root (spinal accessory fibres).

By the Nissl method the cells of the anterior horn appear numerous, and for the most part well stained. Here and there individual cells may show some chromatolysis, but the greater part of the cells are normal, both as to number and character. (Figs. 5 and 6.)

By the Weigert-Pal method the cord appears normal for a child of this age, although the pyramidal tracts are not fully medullated.

By the Van Gieson method there is no evidence of vascular or interstitial change.

Brain.—No change could be found in the cortex of the cerebral hemispheres, in the cerebellum, or in the pons. In the medulla a few degenerate fibres can be seen in the intramedullary course of the twelfth nerve.

The peripheral nerves, the right phrenic, the left sciatic, the right median, examined by the Marchi method, do not show any degeneration, and also appear normal by other methods of examination.

The biceps muscle does not show any marked change. The muscle-fibres are in the infantile condition, uniform in size, there is no fibrosis, and the intramuscular nerves are relatively well stained.

The result of the examination of this case is to show that degeneration has taken place in the lower motor neurons. The changes present are similar to those seen in diphtheritic paralysis—viz., a marked degeneration of the myelin sheath, as shown by the Marchi method, and comparatively little change in the cells of the anterior horn.

Case 2.—William G., aged 5 weeks, was admitted to the National Hospital under the care of Dr. Beevor. The child was the eighth of eight children, four of whom had been similarly affected, viz., the first died at $4\frac{1}{2}$ months, the second died at 8 months, the fourth died at 7 months, and the eighth (the patient) died at 2 months.

The child was full term, there was difficulty with the labour, and he was noticed to be paralysed at birth.

On examination there was complete flaccid paralysis of all four limbs, with the exception of very slight involuntary movements of the fingers of the left hand. Sensation was said to be lost on the limbs and on the trunk to the second rib. All the deep reflexes were absent.

The pathological examination showed no macroscopic change, but on microscopic examination atrophy of the cells of the anterior horns (figs. 7 and 8) and degeneration of the posterior columns were found.

For a full clinical and pathological report of this case see BRAIN, 1902, XXV, p. 85.

Case 3.—Edward T., aged 4 months, was admitted to the Children's Hospital, Great Ormond Street, under the care of Dr. Penrose, in October, 1901.

History.—General helplessness was first noticed one week after birth, and had steadily increased since. The limbs wasted and the breathing became difficult. There was some difficulty in swallowing at times. The child is the fourth of four children. The first is alive, aged 4, and is well. The third child died at 5 months and is said to have had a similar condition to the present patient.

Present condition.—The child lies on its back, crying feebly, but employing all its facial muscles. There is no facial asymmetry. The thorax is quite motionless in breathing; while the abdomen moves freely. There is marked wasting of the shoulder muscles and those of the limbs. The child can apparently do nothing except make a slight movement of the toes. The forearm can be feebly flexed and extended and all movements of the upper arm are capable of being feebly performed, though the child does not raise the arms above the shoulders. The wrists are dropped. The child is absolutely unable to sit up, and when raised the head falls about helplessly. Fibrillary tremor is noticed in the muscles of the arm. The movements of the tongue and eyes appear normal. The deep reflexes are absent and the plantar response, when it can be elicited, is in the direction of the extension of the small toes. The child died. No *post-mortem* was obtainable.

Case 4.—Percy B., aged 6 months, fourth of four children. One died of fits at 4 months, due to injury at birth. One died of tuberculosis. The boy was born at full term, and the labour was natural. He was said by the mother to be healthy at birth. When 4 months old it was noticed that the child could not move the arms. The onset seems to have been quite gradual.

On admission to hospital the child was well nourished, lay on its back taking notice of all around it, smiling, and seemed quite intelligent.

Both arms lay by the side absolutely flaccid, except for some movements of the fingers. Both legs were quite flaccid and powerless. Respiration was almost entirely abdominal, and there seemed to be paralysis of the intercostals. The neck muscles were quite powerless. All the deep reflexes were absent; superficial reflexes indefinite. Sensation apparently perfect. On electrical examination practically no contraction could be obtained to faradic stimulation, except in the flexors of the fingers, and then only with a current which will produce a tetanus in the muscles of a normal individual. To galvanism no definite contraction obtained.

The fundus of the eyes was examined and appeared normal. The child developed broncho-pneumonia and died. No autopsy was obtainable.

The clinical features which this child presented seem to be almost typical of the progressive muscular atrophy of infants, but without the verification of a *post-mortem* the case loses much of its importance.

Case 5.—H. Clarke, aged 8 months, was the third of three children, the other two being healthy. The child had been breast-fed; he had had no difficulty in swallowing and had had no illness. The birth of the child was natural. The history was that the child had always been weak and had never been able to sit up, nor could he hold up the head. The weakness seems to have increased, and when first seen, besides the weakness of the neck muscles above described, the arms were perfectly flaccid, the deltoids being especially weak. The legs were flaccid, only the slightest movement being possible. The knee-jerks were present, but only obtained with difficulty, and the plantar usually gave a flexor response.

There was marked weakness of the back, with a lateral curvature, the concavity being to the left. The pupils were equal.

The child developed broncho-pneumonia and died in a few days.

At the autopsy there was extensive broncho-pneumonia. There was a marked lateral curvature of the spine to the left. The spinal cord and membranes appeared normal. There was no wasting of the cord. Brain appeared normal. All the muscles very pale, but not atrophied. Diaphragm looked a good colour.

Pathological examination.—The cord was examined by the Marchi, Nissl, and Van Gieson methods. The cells of the spinal cord appear to be fairly numerous, and show only slight chromatolysis. In most of the cells the nucleus is centrally placed. The anterior nerve-roots do not appear unduly small.

Examination by Marchi method shows a certain amount of degeneration in the anterior roots very similar to that found in the Case 1, but to a far less degree.

There was in this case no microscopical examination of the peripheral nerves or muscles.

Case 6.—R. A., a boy, aged 3½, was admitted into the Hospital for Sick Children, Great Ormond Street, under the care of Dr. Garrod, June, 1910. He was one of twins; the other (a male) is healthy. This child cut his first tooth at 8 months, and learnt to talk early. The boy never learnt to sit up, and when 15 months old it was noticed that he could not move his legs. He, however, moved his arms quite well. When 2½ years old he was seen by a surgeon, who ordered him a Phelps' box in which he was kept lying down.

The boy is the result of the fifth pregnancy. The eldest child, aged 15, is alive. There has been one miscarriage and two children stillborn.

The boy lies on his back and he can be freely moved about without pain. He is intelligent and can talk well. There is no affection of the ocular nerves. He is quite unable to sit up, nor can he maintain the sitting posture when sat up. He can, however, hold up his head. He can move the arms about fairly well, but there is some contraction of the outer phalangeal joints which limits his movements. There is a peculiar "athetoid" movement of both hands, and when he grasps an object he overdoes the action. The legs lie flaccid in bed, but the right knee-joint cannot be extended more than 35°. The legs are generally wasted and flabby and there is wasting of both lower limbs, especially above the knee, and this is rather more marked on the right side than the left. The right thigh is adducted and the adductor muscle is contracted. There is genu valgum and talipes valgus on the right side. There is no power of movement in the lower limbs, but they can be freely moved passively, and there is marked flaccidity, except for the contraction above mentioned.

There was well-marked lateral curvature in the lower dorsal region, with convexity to the right. The muscles of the back were wasted. There was no tenderness.

The left knee-jerk was present, the right was absent. No plantar response was obtained. The abdominal reflex was present on the left, absent on the right side. Sensation was perfect. Electrical examination showed greatly diminished excitability to both faradic and galvanic current.

I saw the boy in June, 1910, and from the clinical features came to the conclusion that the case was probably one of old and extensive poliomyelitis. I failed to recognize the progressive nature of the case and attributed his continued weakness to the fact that he had been kept for a year in a Phelps' box. On July 8 he had some retention of urine, which was relieved by the catheter. This retention passed off on the 12th. X-rays showed no disease of spine.

On August 24 intercostals became very weak. Broncho-pneumonia developed, and the child died on September 3.

The *post-mortem* showed some patchy broncho-pneumonia. The brain and spinal cord appeared normal to the naked eye, except that the anterior roots appeared smaller than normal. The posterior roots were well developed. The spinal cord was examined by the Marchi, Weigert-Pal, Nissl, and Van Gieson methods.

By the Marchi method practically no recent degeneration could be found. There were in the grey matter of the anterior horns in the cervical region a few fibres which showed degeneration, but they were very few in number.

By the Weigert-Pal method the whole of the white matter of the antero-lateral tracts was paler than the posterior columns, but no tract could be said to be definitely affected. There was no diminution in the size of the grey matter, and the medullated fibres in the grey matter appeared fairly normal. The most striking feature was the smallness of the anterior roots as compared with the posterior, and the great diminution of fibres. The most marked change was to be seen in sections stained by the Nissl and Van Gieson methods. The absence of cells in the anterior horns, both in the lumbar, thoracic and cervical region, is most striking. In any given section one or two normal cells can generally be seen, but the other cells are small, apparently well formed, but only about half the size of the normal cell. Many cells must have entirely disappeared. If the number of cells of moderate size are counted in a series of sections in the lumbar region, they average out about ten to a section, whereas the normal average out to about forty, and these figures do not truly represent the state of affairs, for the size of the cells in this cord is somewhat smaller than in the normal cord. (Figs. 9 and 10.)

Case 7.—Hetty M., aged 3, the youngest of four healthy children, was admitted to the Children's Hospital, Great Ormond Street, under the care of Dr. Voelcker, in October, 1908. She was healthy at birth, and well up till ten weeks ago, when it was noticed one morning that she was unable to walk properly and fell backwards into a sitting position after taking a few steps. On stooping she was unable to regain the upright position. She had incontinence of urine and fæces. The arms were said to be unaffected and the child was able to feed herself. There had been no constitutional symptoms.

Seven weeks later the arms became weak, causing her difficulty in feeding herself. There was irritability, but no evidence of pain.

She is a bright, intelligent, and well-nourished child. She can move her legs, but cannot stand. There is weakness of both deltoids, but the forearm muscles are good. The cranial nerves, optic discs, and trunk muscles are

normal. Sensation is unimpaired. All the deep reflexes are absent, but the abdominals are present and the plantars give an indefinite response.

When at first in the hospital there was a definite increase of muscular weakness. The arms became powerless, only movements of the fingers and slight movements of the wrists remained. The back muscles were weak, and there was a curvature, with the convexity to the right. The legs became weaker and more wasted. A definite weakness of the right side of the face developed. This passed off in a few days. There was the reaction of degeneration in the muscles of the lower limbs.

In December, some two months after admission to the hospital, there was a gradual improvement, so that the child could now get the hand up to the mouth and move its legs. The knee-jerks were still absent. This improvement was maintained till February, 1909. The weakness then again began to increase, the intercostal muscles and diaphragm became affected, and in October, 1909, the child died, twelve months after admission to the hospital, and fourteen months after the onset of the disease.

On *post-mortem* examination nothing abnormal to the naked eye could be found in the brain or spinal cord.

The cord and medulla were examined by the Weigert-Pal, Nissl, Marchi, and Van Gieson methods.

The cord examined by Weigert-Pal method appeared perfectly normal.

By the Marchi method: There was scattered degeneration throughout the length of the spinal cord. The amount of the degeneration was slight, and could not be said to affect any particular tract of the cord. If anything, the anterior and posterior roots in their passage through the white matter of the cord were rather more affected than other parts. There was a little fine degeneration in the grey matter in the region of the anterior horns. The intramedullary portions of the twelfth nerve also show some fine degeneration. The extramedullary portion of the anterior and posterior roots practically show no change.

By the Nissl method: The cells of the grey matter are well stained. Many of the cells of the anterior horns in the lumbar, thoracic, and cervical regions of the cord appear perfectly normal. Some cells, however, in each region of the cord show chromatolytic changes. These changes are not confined to any one group of cells, but affect individual cells in any group, a cell in close proximity being perfectly normal. (Figs. 11 and 12.)

The changes which these cells exhibit are a somewhat swollen appearance, the nucleus being eccentric, but the nucleolus well stained.

The chromophylic substance of the cells stains diffusely, and it is only at the margin of the cell that the normal chromophylic granules can be seen.

There are very few cells that can be said to be in a state of profound degeneration, and in most of those affected the change is comparatively slight.

The cells of Clarke's column also show some changes.

By the Van Gieson method: The interstitial tissue and the vessels of the cord appear perfectly normal, and there is no evidence of either past or present inflammation.

The peripheral nerves examined were those of the sciatic and brachial plexus.

By the Marchi method: A very considerable amount of degeneration of the myelin sheath could be seen. This was more marked in the nerves of the brachial plexus than in the sciatic.

By the Van Gieson method: The same nerves appear perfectly normal, and there is no evidence of interstitial inflammation.

The muscle-fibres of the diaphragm show most marked fatty degeneration when stained by the Marchi method.

The changes found in this case point to a toxic degeneration of the lower motor and sensory neurons. Since the changes are more marked in the peripheral nerves than in the cell body, the case would fall into the group known as toxic neuritis. The clinical course and symptoms do not, however, correspond with those commonly associated with that disease.

Case 8.—Matilda L., aged 11. Twelve months, weakness of hands. Seven months, unable to button clothes. Four months, weakness of legs. Two months, adenoids removed, and much worse since that operation. Fourteen days, pain in back, and increasing difficulty in swallowing.

Intelligent, deaf, some atrophy of tongue, palate moves well on phonation, weakness of neck, respiration thoracic, upper intercostals only in use. Claw hand, wrist-drop. Weakness of upper arm and shoulder muscles. Can walk, but only feebly. Knee-jerks brisk, plantar flexor, sensation natural to all forms.

Electrical reaction R.D. in some muscles, in others only diminution of irritability. Sudden death from respiratory failure six months later, eighteen months after onset of disease.

Pathological examination showed an extensive destruction and atrophy of the cells of the anterior horn, from the upper cervical to the lower thoracic segment, extensive degeneration of the whole of the ventral region of the cord in the thoracic segments. Degeneration of the direct cerebellar tracts both dorsal and ventral.

There was a marked increase of the connective tissue in the ventral portion of the cord in the thoracic region.

The walls of the vessels showed no change. The cord showed both recent and old degeneration.

The change in the cord is attributed to a chronic myelitis secondary to some vascular change and toxic blood state. For full clinical and pathological report of the case, see BRAIN, 1903, xxvi, p. 473.

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THE INDEPENDENCE OF THE PERIPHERAL SENSORY NEURONE IN VIEW OF THE RESULTS OF EXPERIMENTAL SECTION OF THE OPTIC NERVE IN THE RABBIT.[1]

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PART I.—INTRODUCTION.

PART II.—PRESENT INVESTIGATION.

A. Results of Experimental Section of the Optic Nerve.

(i) Operative Technique.
(ii) Histological Methods.
(iii) Experimental Details.
(iv) Discussion of Results.

B. Results of Autolytic Experiments.

(i) General Remarks.
(ii) Experimental Details.
(iii) Discussion of Results.

PART III.—CONCLUSIONS.

PART I.—INTRODUCTION.

ALTHOUGH in the general sense one may accept the neurone theory, viz., that the nervous system consists of innumerable anatomically independent cellular units, the processes of which exist in contiguity, but not continuity, with each other [39], the mutual relationship and interdependence of the neurones is a problem as yet unsolved. This is specially the case as regards the peripherally placed neurones. The object of the present investigation was to throw light upon the question. The retinal neurones were selected for the purpose of experiment, the plan being to separate them from their central connexion by section of the optic nerves, without interference with the vascular supply of the retina.

In the retina the cells of the peripheral neurones are those of the outer and inner nuclear layers, and, although the small size of these neurones renders them more difficult of observation than could be

[1] The expenses of this research were defrayed by a grant from the Carnegie Trustees.

desired, yet the comparative simplicity of their structure makes the histological examination tolerably easy.

The cells of the ganglionic layer, on the other hand, are conspicuous by their size and structural definition, and their condition was studied in each experiment.

Ontogeny of the Visual Peripheral Sensory Neurone.

The retina develops as a hollow outgrowth from the primitive forebrain, the stalk which connects these two structures persisting as the optic nerve. The ganglion cells are the cells of the innermost cellular layer, and are in connexion with the optic nerve-fibres which conduct stimuli through the various stations of arborization (corpora quadrigemina, corpora geniculata externa, and optic thalamus) to reach the visual cortex. The retina, optic nerve and optic tract are thus developmentally part of the central nervous system.

With regard to the relations of the retinal elements, two views are held. According to the one which is advocated by Barker [4] the bipolar cells of the inner nuclear layer are analogous to the spinal peripheral neurones of the dorsal roots, the ganglion cells of the retina corresponding to neurones of the second order (*i.e.*, the neurones of the grey matter of the spinal cord). One must not drive such a comparison too far, and the alternative view, that the ganglion cells of the retina are analogous to the dorsal spinal ganglia, is more generally accepted. The bipolar cells of the inner nuclear layer are the peripheral sensory neurones which have their peripheral processes in contact with the central process of the still more peripherally situated cells of the external nuclear layer. It is the aim of the present investigation to follow the fate of the neurones situated distal to the site of injury in the optic nerve.

Owing to limitations of space it is impossible to give a critical review of the general literature bearing upon the present research; a bibliography of the more essential of the published works will be found at the end of this paper. With regard to the experiments performed by other workers, section of the optic nerve has formed the subject of numerous publications. The results of these experiments are of little or no assistance to us, since the purposes for which the investigations were instituted were other than the present, and the histological methods—of the earlier workers at least—were inappropriate. An exception, however, is to be made in the case of Birch-Hirschfeld

[8], who published in 1900 the first of a series of retinal experiments, including section of the optic nerve.

The value of his work is enchanced by the fact that he employed the Nissl method, and described the fine histological appearances in minute detail, so that his results have been taken as a guide in the present investigation. He covered a wide field in his experiments, investigating the behaviour of the retina in the rabbit under the influence of different pathological conditions, viz., electrical and thermal stimulation, section of the optic nerve, and poisoning with various drugs (methyl-alcohol, nicotin, quinine, &c.).

The results he obtained from section of the optic nerve must now be summarized more or less in detail.

His operations were performed as far back as possible in the orbit, in order to avoid injury to the vessels. In some cases he operated from above, by means of a knob-pointed knife, and, although the operation was practically bloodless, the ophthalmoscope showed almost immediate contraction of the retinal arteries. In one case he cut the nerve intracranially, close to the optic foramen.

In his anatomical investigation he found considerable divergence from the normal fifty-five hours after operation, when chromatolysis had already begun in the case of the ganglion cells. The chromatin clumps had lost their sharpness of outline. The nucleus was large, swollen, diffusely stained, and often almost touched the cell wall. The cells of the internal nuclear layer were small, full of chromatin, and often irregular in outline. The cells of the outer nuclear layer were roundish, devoid of edge-crenation, and showed only partial cross-striping. Cases examined at five, ten, and fifteen days after operation revealed still further advanced chromatolysis, shrinking of the ganglion cell (shown by the increased pericellular space) and its nucleus. The normal Nissl granules had been replaced by a darkly staining, badly defined, crumbling mass, or were altogether wanting, their place being taken by vacuoles of different sizes. He emphasized the fact that these vacuoles were absent from the control.

Valuable as are these results, it was felt that as his attention had been chiefly directed to the ganglion cells, and as the object of the present investigation was to study the peripheral neurones, a further series of experiments was desirable.

Part II.—Present Investigation.

A. Results of Experimental Section of the Optic Nerve.

(i) Operative Technique.

The operation was performed with the usual aseptic precautions and under full anæsthesia. The animal having been placed in a good light on the operating bench, the eye to be operated upon (in all cases, except one, the right) was douched with tepid sterile water. The conjunctiva was picked up in dissecting forceps, and was incised in a line parallel to the corneal margin, and situated about 4 mm. from it. This incision extended for about 1 cm. on either side of a point opposite the middle of the supra-orbital margin.

The wound was then deepened by gentle separation of the conjunctiva from the underlying structures, as far back as possible. The superior rectus muscle was sometimes divided, but in many cases this was not necessary. The "corneal" flap of the wound was then grasped in fixation forceps, and the eyeball rotated downwards. By gentle manipulation the eye was raised out of the orbital cavity (it was sometimes necessary to divide the outer canthus at this stage, if the palpebral fissure was small), turned sharply downwards and retained in this position by the assistant. In this way the optic nerve (which in the rabbit enters the sclera above the horizontal meridian) came to lie high up in the wound, and the nerve after a little careful dissection could be isolated. The dense tissue of Tenon's capsule which forms a funnel-shaped investment for the nerve is liable to cause trouble at this stage, and the delicate vessels are easily damaged in making way through it. The nerve appeared as a slender glistening white cord and, having been lifted up on the tenotomy hook, was divided far back (*i.e.*, clear of the central vessels) by means of scissors inserted, closed, and then opened merely enough to include the nerve. When traction was removed, the eyeball readily slipped back into the orbital cavity. Hæmorrhage, when it occurred, as a rule, took place at the stage of deepening the original incision, *i.e.*, in the region of the anterior vessels of the globe. It was usually easily controlled by pressure. The hæmorrhage which was met with when the nerve was divided was no doubt due to the inclusion of some of the branches of the central artery, but was of infrequent occurrence, and was soon controlled. In a few cases ulceration of the cornea ensued, due either to slight abrasion at the time of operation or to an atrophic condition, the result of lesion of

some of the long anterior ciliary nerves. The ulceration subsided in a few days (under boracic douching), leaving a small leucoma.

In all cases total and permanent blindness of the eye appeared to follow from the operation, although the difficulty of estimating the amount of visual perception in a rabbit makes one reserved in any statement regarding the physiological condition.[1]

The pupil, which usually contracted to a pin-point at the moment of division of the nerve, gradually dilated, and remained semi- or fully-dilated and inactive to light. Ophthalmoscopic examination of the fundus never revealed more than some slight narrowing of the retinal vessels, with pallor of the "medullary rays" in the late stages.

The experiments recorded are those in which section of the optic nerve was uncomplicated by injury to the retinal vessels, or by lasting inflammation.

(ii) *Histological Methods.*

In every case the same treatment was adopted for the control as for the experimental material.

Fixation.—For successful demonstration of the Nissl granules, the most satisfactory fixative was alcohol (50 per cent. to 75 per cent.). The tissue remained in this from a half to several hours, according to the size. Dehydration in several changes of absolute alcohol. Clearing was least injurious when carried out in cedar-wood oil. Other fixatives employed, with less satisfactory results, were: $HgCl_2$ (saturated saline solution), formol-saline (10 per cent. formalin in normal saline solution), and picro-formol (saturated watery solution of picric acid 75 parts, formol 25 parts, acetic acid 5 parts).

Staining.—Nissl granules in every case were stained by toluidin blue, no counter-stain being employed. (Methylene blue and thionin did not yield good results.)

Other stains for general demonstration were hæmalum and eosin; and Weigert's rapid iron-hæmatoxylin method.

Silver impregnation.—The chrome-silver method of Golgi was unsuccessful in these experiments, although a fair amount of success was obtained in the case of the ox-retina.

The method of Cajal (formula II) produced very beautiful results in

[1] The method adopted was that of flashing the brightly illuminated ophthalmoscopic mirror on to the eye in the dark room. The response which, in the case of the control, was immediate, although not very vigorous, and consisted in twitching of the eyelids and shunning of the light, was found to be entirely absent in the operated eye.

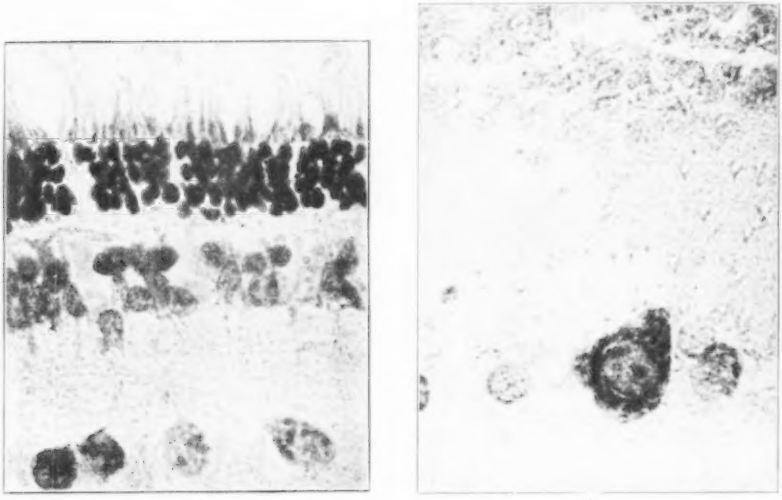
many cases, but was seldom satisfactory in control and experimental material of the same case.

Cox's method of sublimate and bichromate impregnation was not found satisfactory.

Ehrlich's intra-vitam method (Dogiel's modification) of methylene blue impregnation was employed successfully in one or two cases, but was not of much practical value in these experiments.

(iii) Experimental Details.

Experiment I.—Adult albino. Thirty-four hours after operation no microscopic changes were discovered in the operated eye.



(*a*) (*b*)

FIG. 1.—Experiment II. Forty-eight hours after section of the optic nerve.

Operated. Tol. B. Photomic. × 1,000. Showing ganglion cells somewhat diffusely stained. In the one to the left the nucleus is eccentric. The outer retinal layers are normal.
Control. Tol. B. Photomic. × 1,000. Showing large ganglion cell with discrete chromatin granules and centrally placed nucleus. The outer layers are not seen.

Experiment II.—Adult albino. Forty-eight hours (fig. 1). Operation practically bloodless. No inflammation ensued. Fixation of retina in 50 per cent. alcohol and in 10 per cent. formalin. Sections stained by toluidin blue and by Weigert's iron-hæmatoxylin method. Impregnation by Cajal's silver method was unsuccessful.

Microscopic examination.—The outer layers of the retina showed no abnormality in the operated eye. The nuclei of the rods showed the chromatin arranged in the usual form of twin masses separated by a considerable interspace—an arrangement which may be described by the term "cross-striping." The fine serration of the edges of these masses, due to the presence of fine strands of chromatin passing out to the cell membrane across the intervening space, for convenience of description may be designated as "cog-wheel" markings. In the operated eye these features were as distinct as in the control. The larger and more complex nuclei, generally looked upon as belonging to the cones, showed no variation from the normal, having the typical arrangement of the chromatin (*i.e.*, three or four masses with cruciform interspace). They were much less numerous than the rod-nuclei. The cells of the internal nuclear layer were normal and showed the chromatin arranged in the form of a loose, tangled, granular skein or network.

With regard to the cells of the ganglionic layer, a certain amount of blurring of the outline of the Nissl bodies was met with in the operated eye. Considerable variation in staining power was to be seen in the control, instances of cells in which the protoplasm was deeply and diffusely stained being fairly common. Most of the cells, however, in the control showed a high degree of differentiation of chromatin which was practically never met with in the operated eye.

The fact that one found in the normal many cells exhibiting the phenomena which, in the case of the cells of the central nervous system are usually classified as pathological (viz., eccentric position of the nucleus, diffuse staining of the protoplasm with blurring of Nissl bodies, vacuolation, enlargement of pericellular spaces), led to the conclusion that such phenomena must either be due to artefacts or that they were themselves an expression of phases of functional activity.

Experiment III.—Adult black-and-white rabbit. Forty-eight hours. Operation practically bloodless. No inflammation ensued. Fixation in 10 per cent. formol-saline and in Müller's solution. Staining by toluidin blue and Weigert's iron-hæmatoxylin method.

Microscopic examination.—The ganglion cells in both retinæ were frequently profusely vacuolated, and pericellular spaces were well marked. The chromatin granules showed little or no variation from the normal, but the number of atypical cells (*i.e.*, those which show diffuse staining of the protoplasm, vacuolation, &c.) was greater for the operated than for the control eye. The outer layers were unchanged.

Experiment IV.—Adult albino. Seventy-two hours. There was some hæmorrhage early in the operation, which was easily controlled. No inflammation ensued. Fixation in 50 per cent. alcohol. Staining by toluidin blue and hæmalum and eosin. Silver preparations unsatisfactory.

Microscopic examination.—In the sections the line of division was seen to be behind the entrance of the vessels into the nerve. The ganglion cells were on the whole well preserved, some of them showing fairly well defined chromatin bodies. There was, however, evidence of a certain amount of shrinking in the cells of the operated eye as compared with the control. In the cells of the latter there was a clear space around the nucleus, whereas in those of the operated eye this space was often reduced by the shrinking of the cell, so that the cell appeared as a more or less dense ring-like band of chromatin encircling the nucleus. The cells of the outer layers showed no variation from normal.

Experiment V.—Adult black-and-white rabbit. Four days (fig. 2). Operation without hæmorrhage. No inflammation followed. Fixation in 50 per cent. alcohol. Staining with toluidin blue. Silver impregnation successful for the operated, unsuccessful for control.

Microscopic examination.—There was on the whole no great abnormality in the operated retina. There were often tolerably well preserved cells in the ganglionic layer, but definitely "normal" cells occurred only in the control. The outline of the chromatin bodies was not at any time so sharp in the operated eye as it was in the control, and there was evidence of condensation and shrinkage in many of the cells. The other layers were normal. The silver preparations in the operated eye showed numerous fine varicosities in the fibrils of the internal plexiform layer. The broad, ribbon-like bands of the external layer were well demonstrated. The silver preparations of the control also were successful.

Experiment VI.—Adult black rabbit. Seven days. There was slight retrobulbar hæmorrhage at time of operation, and slight transient conjunctivitis ensued. At the time of death the eye appeared normal. Fixation in 50 per cent. alcohol and Müller's solution. Staining by Weigert's iron-hæmatoxylin method and toluidin blue. Silver preparations were successful in both control and operated eye, but no striking difference was revealed by this method.

Microscopic examination.—In the ganglion cells of the operated eye the chromatin granules were small and had a tendency to become

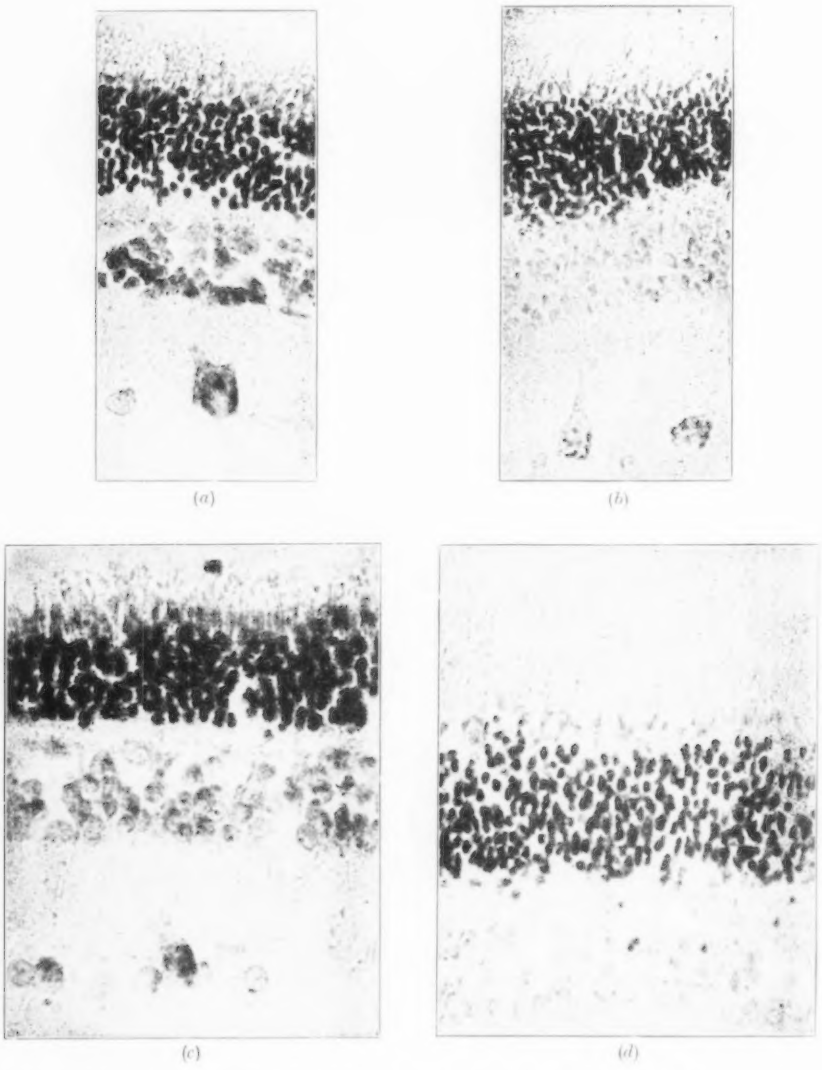


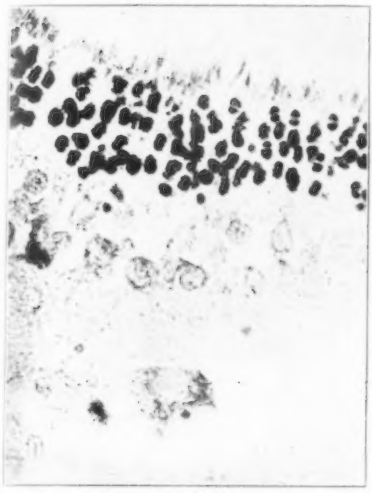
FIG. 2.—Experiment V. Four days after section of the optic nerve.

(*a*) *Operated.* Tol. B. Photomic. × 700. Showing large ganglion cell with somewhat diffuse staining. The outer layers are normal.

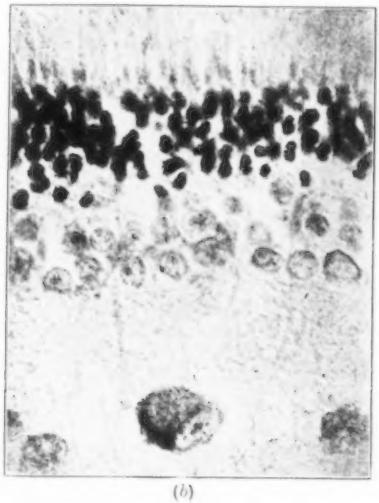
(*b*) *Control.* Tol. B. Photomic. × 500. Although under lower magnification than (*a*), the ganglion cells show much greater detail of structure. The outer layers contrast rather unfavourably with those of (*a*).

(*c*) *Operated.* Tol. B. Photomic. × 950. To show normal outer layers.

(*d*) *Control.* Tol. B. Photomic. × 950. Outer layers compare unfavourably with (*c*).



(*a*)



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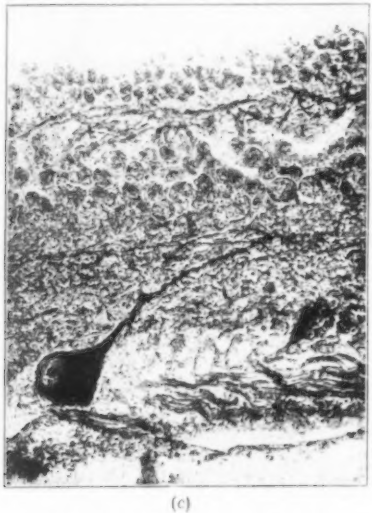


(*c*)

FIG. 3.—Experiment VII. Eight days after section of the optic nerve.

(*a*) *Operated.* Tol. B. Photomic. × 1,000. Showing outer layers normal. Note well-marked "cross-striping" and "cog-wheel" in the outer nuclear layer.

(*b*) *Control.* Tol. B. Photomic. × 1,000. Showing outer layers which are, if anything, less "normal" than in (*c*).

(*c*) *Operated.* Silver impreg. Photomic. × 800. Shows large ganglion cell with dendrite passing upwards to inner plexiform layer. The axon becomes continuous with an optic fibre (below).

broken up into fine dust. When the granules were large they had rather badly defined edges. Occasionally large, fairly well preserved ganglion cells were met with, but they were never so large or so well differentiated as the large cells of the control. The other layers were normal.

In the silver preparations the varicosities of the fibrils of the cellular processes were most marked in the operated eye, being almost absent in the control. The processes of the "horizontal cells" of the internal nuclear layer were specially well demonstrated in the control.

Experiment VII.—Adult albino. Eight days (fig. 3). Operation bloodless. Fixation in 50 per cent. alcohol, and in Müller's solution. Silver impregnation successful in the operated eye, failed for the control. Staining with toluidin blue and Weigert's iron-hæmatoxylin.

Microscopic examination.—Well-preserved ganglion cells occurred much less frequently in the operated eye than in the control. The cells of the former were usually pale-staining, with finely divided chromatin. The pericellular spaces were more pronounced in the control than in the operated eye. The outer retinal layers were normal. In the silver preparations varicosities were occasionally met with in the fine fibrils of the inner plexiform layer. The fibrils of the external plexiform layer were seen to end in a rich anastomosis around the cells of the external nuclear layer. The protoplasmic processes of the ganglion cells were devoid of varicosities.

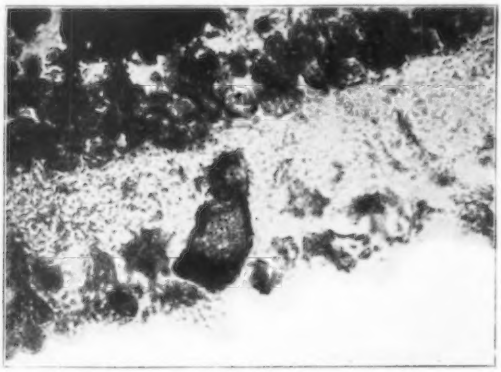
Experiment VIII.—Adult albino. Three weeks (fig. 4). There was slight hæmorrhage during the operation and a corneal ulcer developed. This cleared up, and, at the time of death, a small scar only remained on the otherwise healthy looking cornea. Fixation in 50 per cent. alcohol. Staining with toluidin blue; hæmalum and eosin.

Microscopic examination.—In the control the number of "atypical" ganglion cells in this case was considerable, but at the same time there was a preponderance of typical cells. In the operated eye, on the other hand, one rarely, if ever, met with a typical ganglion cell, the best preserved cell consisting usually of a peripheral ring of small bead-like granules surrounding a densely stained nucleus. The outer layers were normal.

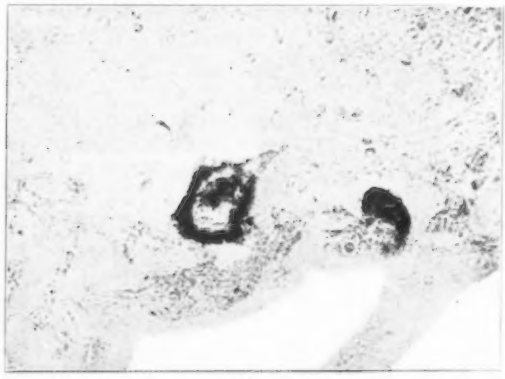
Sections stained with hæmalum and eosin showed the presence of a considerable amount of inflammatory exudate with giant cells around the stump of the optic nerve. It is probable that the pronounced atrophy of the ganglion cells in this case was partly due to the inflammatory conditions and not solely to division of the nerve, although

from the fact that the outer layers were unaffected we did not reject the experiment.

Experiment IX.—Adult albino. Three weeks (fig. 5). Operation almost bloodless. No inflammation ensued. Fixation in 50 per cent.



(*a*)



(*b*)

FIG. 4.—Experiment VIII. Three weeks after section of the optic nerve.

(*a*) *Operated.* Tol. B. Photomic. × 1,000. Note the diffusely staining ganglion cell with what appears to be the extruded nucleus (above).
(*b*) *Control* as in (*a*). Large typical ganglion cell in centre; small cell to the right, showing degeneration (eccentric extruded nucleus and rupture of cell).

alcohol, in a saturated solution of $HgCl_2$ and in 10 per cent. formol-saline. Staining with toluidin blue.

Microscopic examination.—(i) Tissues fixed in $HgCl_2$. The ganglion cells were smaller in the operated eye than in the control. The Nissl

granules were almost entirely absent from the operated eye. Vacuolation and enlargement of the pericellular spaces occurred with no greater frequency in the operated than in the control eye. The outer layers were normal.

(ii) Fixation in 50 per cent. alcohol. There was a general tendency

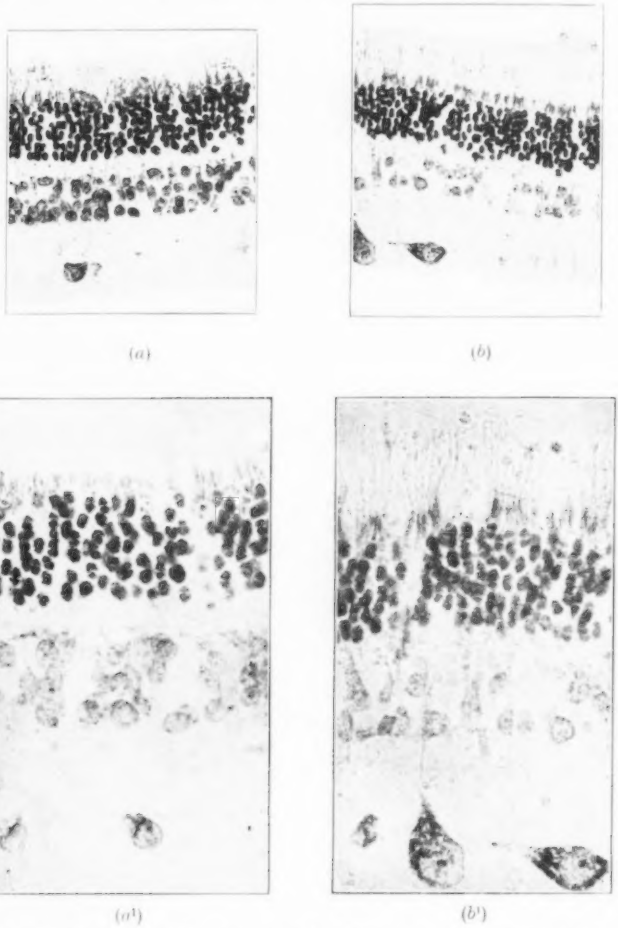
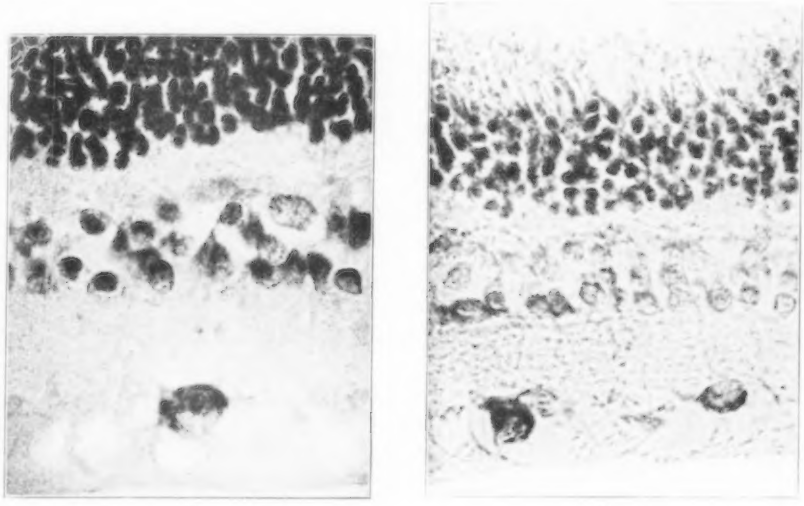


FIG. 5.—Experiment IX. Three weeks after section of the optic nerve.

(*a*) *Operated.* Tol. B. Photomic. × 400. Shows small ganglion cells which are somewhat diffusely stained and have feeble processes. The outer layers are normal.
(*a*¹) Same. × 1,000.
(*b*) *Control* as in (*a*). Showing normal ganglion cells, and outer layers.
(*b*¹) Same. × 900.

to clearer definition in the cells than was the case in fixation with $HgCl_2$, but the same relative differences existed between the two eyes as in the former.

(iii) Fixation in formol-saline. There were appearances of pronounced vacuolation in the ganglion cells of both eyes. The sharpness of intranuclear definition was less than that obtained by employment of either of the preceding methods, but the difference between the ganglion cells of the two retinæ was maintained as in the former.



(*a*) (*b*)

FIG. 6.—Experiment X. Six weeks after section of the optic nerve.

(*a*) *Operated.* Tol. B. Photomic. × 1,000. The ganglion cell in the lower part of the field shows somewhat diffuse staining. The outer layers are practically normal, the nuclei of the rods and cones showing a well-marked "cross-striping" and "cog-wheel" arrangement.

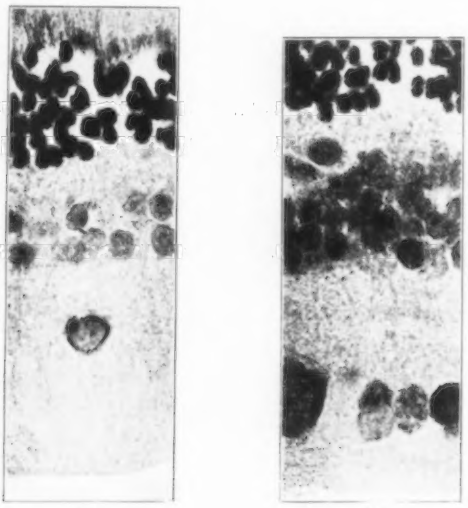
(*b*) *Control.* × 950. To show outer layers with normal appearances.

By the formol-saline method of fixation one saw particularly well demonstrated the cells of the innermost stratum of the internal nuclear layer (? amacrine cells of Cajal) which were arranged at intervals from one another, each cell showing a distinct downgoing protoplasmic process containing chromatin. These cells were slightly more conspicuous in the operated than in the control eye, and were possibly in connexion with centrifugal fibres.

Experiment X.—Small white rabbit. Six weeks (fig. 6). Operation

practically bloodless. Slight corneal inflammation ensued which resulted in a small leucoma at the lower part of the cornea. At the time of death the eye seemed otherwise normal. Fixation in 50 per cent. alcohol. Staining with toluidin blue and with hæmalum and eosin. Silver impregnation unsuccessful.

Microscopic examination.—In the hæmalum and eosin specimens the ganglion cells of the operated eye were seen to be much reduced in size,



(*a*) (*b*)

FIG. 7.—Experiment XI. Fifteen weeks after section of the optic nerve.

(*a*) *Operated.* Tol. B. Photomic. × 1,000. Note the solitary ganglion cell having a scanty ring of protoplasm around the centrally situated nucleus. The cells of the inner nuclear layer are normal. The cells of the outer nuclear layer are densely stained and show less definition than in the control, but still show indication of "cross-striping" and "cog-wheel" arrangement.

(*b*) *Control* as in (*a*). Showing deeply stained ganglion cells alternating with others which tend to become rarefied. Note well-defined "cog-wheel" markings of outer nuclear layer. In this case the slides to be photographed were not from strictly the same regions in both, as will be seen from the marked preponderance of ganglion cells in the control, but the points illustrated are borne out in all the other sections examined.

The nucleus was often all that remained to represent the cell. These nuclei were irregular in outline and were very densely stained. In the toluidin blue specimens the cell body was diffusely stained, or the chromatin was in the form of dust-like particles. The cell processes were attenuated and tapered off sharply close to the cell body. The cells of the internal and external nuclear layer appeared normal, except

for the fact that occasionally the cone nuclei in the operated appeared somewhat smaller than in the control.

Experiment XI.—Adult albino. Fifteen weeks (fig. 7). There was practically no hæmorrhage during the operation. No inflammation ensued. Fixation in 50 per cent. alcohol, in saturated solution of $HgCl_2$, and in formol-saline 10 per cent. Staining with Weigert's iron-hæmatoxylin and toluidin blue.

Microscopic examination.—(i) $HgCl_2$ fixation. The ganglion cells of the operated eye were very much shrunken, and were diffusely stained. Differentiation into granules was scarcely ever met with, the ground substance being always diffusely stained. Vacuolation when present was less frequent in the operated than in the control eye. Pericellular spaces were not well seen. There was slight impairment of "cog-wheel" marking in the cells of the outer nuclear layer, but "cross-striping" was present. Inner nuclear layer normal.

(ii) Fixation in 50 per cent. alcohol. Occasionally the affected ganglion cells showed indication of granular structure, but at best the granules were small and dust-like. The pericellular spaces were more conspicuous than in (i), and were of less frequent occurrence in the operated eye than in the control. Vacuolation was rarely seen in either. The cells with their processes were on the whole more sharply outlined both in operated and control than was the case in fixation with $HgCl_2$. No abnormality was to be made out in the inner nuclear layer. The outer nuclear layer showed slight loss of "cog-wheel" marking and "cross-striping."

(iii) Fixation in formol-saline. Vacuolation was rather well marked, occurring on the whole with greater frequency in the control. Staining was not so satisfactory for operated or control as in (i) or (ii).

Experiment XII.—Adult albino. Sixteen and a half weeks (fig. 8). There was slight hæmorrhage during the operation. No inflammation ensued. Fixation in 50 per cent. alcohol. Staining with toluidin blue, hæmalum and eosin. Silver impregnation was highly successful in the control, but failed in the operated eye.

Microscopic examination.—The ganglion cells in the operated retina were much shrunken (although no enlargement of the pericellular spaces was visible). "Normal" ganglion cells were entirely absent. Staining was, as a rule, very diffuse, although occasionally a dust-like condition of the chromatin occurred. In the latter case the dust-like particles were met with in the centre of the cell, and were surrounded by a row of somewhat larger bead-like chromatin granules near the cell

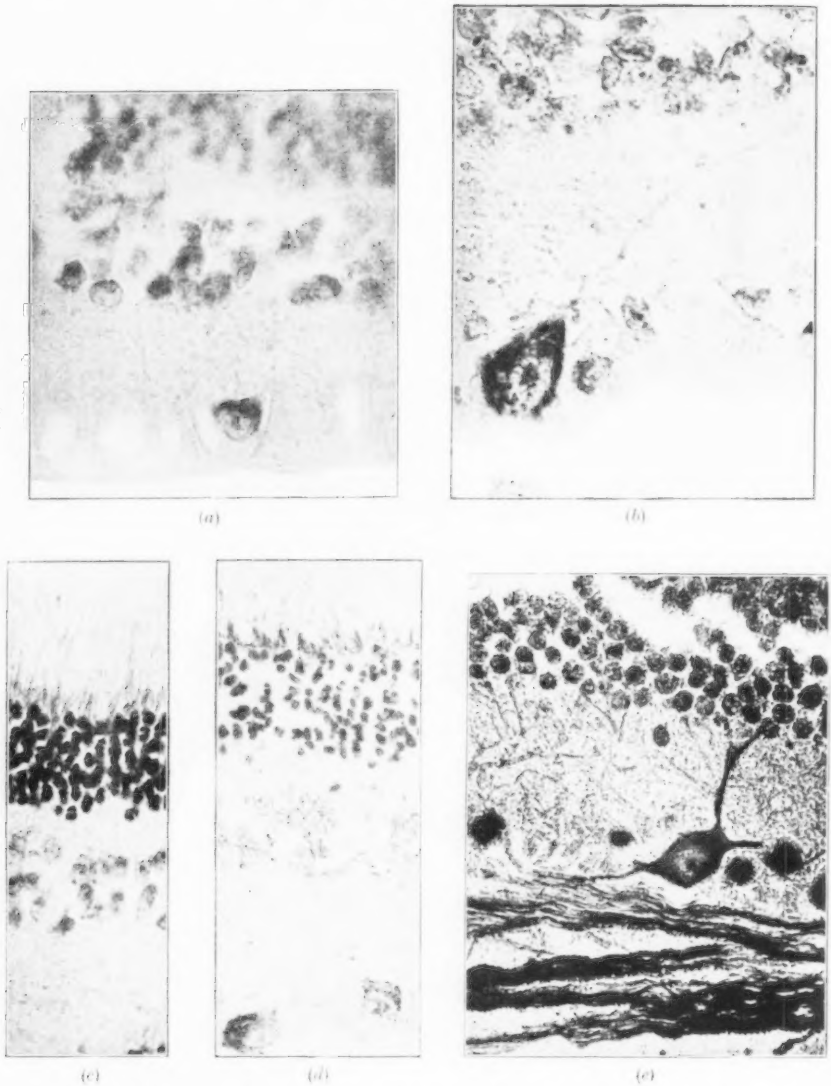


Fig. 8. Experiment XII. Sixteen and a half weeks after section of the optic nerve.

(*a*) *Operated.* Tol. B. Photomic. × 1,000. Showing shrunken ganglion cell. The protoplasm is diffusely stained and the nucleus is somewhat eccentric. The pericellular space is seen. Protoplasmic extensions are scarcely visible (compare (*b*)).

(*b*) *Control* as in (*a*). Showing "normal" ganglion cell, with well-defined up-going process.

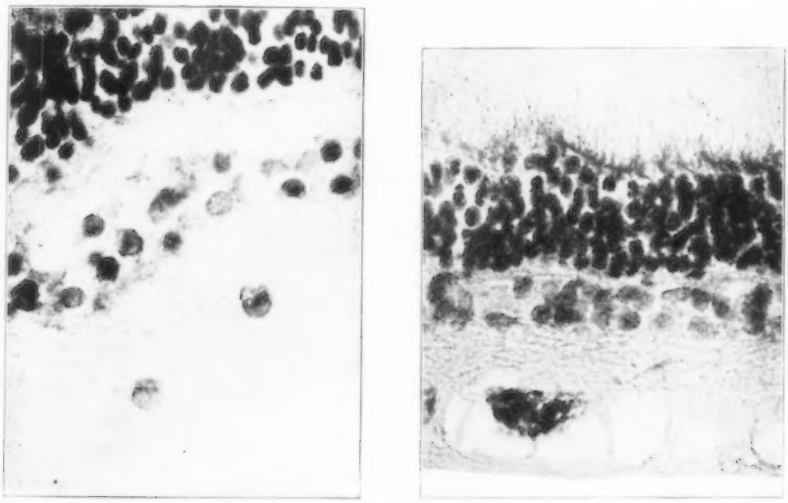
(*c*) *Operated.* Tol. B. Photomic. × 950. Showing outer layers which appear normal.

(*d*) *Control.* Tol. B. Photomic. × 950. Showing outer layers which compare unfavourably with (*c*).

(*e*) *Control.* Silver impreg. Photomic. × 700. Showing large ganglion cell with well-stained processes. The axon is seen passing out (below) to become continuous with an optic nerve-fibre. No varicosities are evident.

margin. The cell processes were much attenuated, being often unrecognizable. The cells of the internal nuclear layer in the operated eye were perhaps paler than in the control, and the cells which were described (in Experiment IX) as being in connexion with centrifugal fibres (amacrine cells) were particularly definite. The cells of the outer nuclear layer appeared unchanged, except for a slight blurring of the chromatin as compared with the control.

Silver impregnation was successful in the control, and it is to be noted that the fibres of the plexiform layers were devoid of varicosities.



(*a*) (*b*)

FIG. 9.—Experiment XIII. Thirty-eight weeks after section of the optic nerve.

(*a*) *Operated.* Formol saline fixation. Tol. B. Photomic. × 1,000. Showing shrunken hyaline ganglion cells with eccentric nuclei. The chromatin is diffusely and densely stained. Their pericellular spaces are not enlarged. Note that although definition of the chromatin in the external nuclear layers is not well marked the corresponding elements in the control show similar characteristics.

(*b*) *Control* as in (*a*). Note ganglion cell showing large well-defined Nissl granules. The cells of the outer and inner nuclear layers show scarcely better definition than those of the corresponding layers in (*a*).

Experiment XIII.—Long-haired adult grey rabbit. Thirty-eight weeks (fig. 9). Operation was practically bloodless. Fixation in $HgCl_2$ and 50 per cent. alcohol. Silver impregnation was unsuccessful. Staining with toluidin blue and Weigert's iron-haematoxylin.

(i) $HgCl_2$ fixation. In the case of the control beautiful fixation of

the ganglion cells was obtained by this method, the Nissl granules being plumper and slightly less well defined than in alcohol fixation. At some parts of the operated retina the ganglion cells were non-existent. At other parts of the retina they were represented, but only by small cells diffusely stained, with eccentric nuclei; or by paler cells with fine dust-like particles of chromatin. The processes of these cells were tapering and ended off sharply close to the cell. The internal nuclei were well preserved. "Amacrine" cells were not conspicuous in these specimens. The cells of the external nuclear layer showed evident "cross-striping" and "cog-wheel" arrangement, and appeared almost normal.

(ii) Formol-saline fixation. Vacuolation was very pronounced, especially in the ganglion cells of the control. Pericellular spaces were no less pronounced in the control than in the operated eye. The ganglion cells in the operated eye were almost universally shrivelled and diffusely stained. Occasionally a large ghost-like cell was met with. Owing to somewhat pale staining of the cells of the internal nuclear layer the "amacrine" cells were often conspicuous. The cells of the external nuclear layer were often lacking in the typical features of cog-wheel marking and cross-striping, but as the same characteristics were met with in the control the defect was probably one of fixation only.

Note.—Of the other experiments performed in this series, three were rejected on account of severe hæmorrhage at the time of operation, the nerve having been divided of necessity rather blindly owing to difficulty in isolating it from the adjacent structures. Two experiments ended in phthisis bulbi. Three cases were discarded on account of unsatisfactory fixation (picro-formol) and eight were lost through the occurrence of incidental disease in the rabbits.

(*iv*) *Discussion of Results.*

A numerical estimate of the cells of the ganglionic layer in the case of the operated eye as compared with the control appeared to be of some value in forming an idea of the proportion of ganglion cells which had perished in the course of the experiment. The method of carrying out the attempt was the following:—

(1) As nearly as could be accomplished the same part of the retina was taken for control and operated eye.

(2) Owing to the difficulty in arriving at an idea of what were cells in a state of perfect preservation as compared with others less well

preserved, the plan was adopted of including all the ganglion cells which were present and could be recognized as such, with a view to finding if there were reduction in their number in the operated eye.

(3) Estimation was made by means of the eye-piece micrometer, the lineal unit being ·2 mm., with ultimate calculation for 1 mm.

Thus we see that throughout the series a considerable reduction was the rule, a reduction which was a confirmation of the descriptive results given in the text. That some disappearance of cells had taken place

TABLE.

No. of experiment	Duration	Number of fields examined		Average cells per ·2 mm.		Average per 1 mm.		Average per 1 mm. in round numbers		Descriptive result in operated eye
		Control	Operated	Control	Operated	Control	Operated	Control	Operated	
i.	24 hours	89	89	2·78	2·74	13·9	13·7	14	14	No material difference.
ii.	48 ,,	45	45	9·20	4·28	46·5	21·4	46	21	Much fewer.
iii.	48 ,,	10	40	3·52	3·70	17·6	18·5	18	18	No change, or slightly more numerous.
iv.	72 ,,	30	30	2·23	3·33	11·1	16·6	11	17	Much more numerous.
v.	4 days	52	52	12·56	4·32	62·8	21·6	63	22	Much fewer.
vi.	7 ,,	60	60	2·30	1·82	11·5	9·1	11	9	Fewer.
vii.	8 ,,	64	64	6·48	5·29	32·4	26·4	32	26	Fewer.
viii.	3 weeks	43	43	8·41	1·93	42·0	9·6	42	10	Much fewer.
ix.	3 ,,	523	523	4·56	3·62	22·8	18·1	23	18	Fewer.
x.	6 ,,	30	30	3·53	2·43	17·6	12·1	18	12	Fewer.
xi.	15 ,,	1,023	1,023	3·85	3·04	19·2	15·2	19	15	Fewer.
xii.	16½ ,,	30	30	2·50	2·06	12·5	10·3	12	10	Fewer.
xiii.	38 ,,	482	482	6·10	2·83	30·5	14·1	30	14	Much fewer.
					Aggregate			339	206	

Note.—(i.) Out of an aggregate of 339 for the control, and 206 for the operated eye, the average in each of the 13 cases may be taken as 26·7 and 15·84 respectively (indicating a marked reduction for the operated eye).

(ii.) The variability in the control ranges from 63 as highest to 11 as lowest, whereas in the operated eye the range is only from 26 to 9.

(iii.) In the control 5 are above 26·7, in the operated eye all are under 26·7. In the control 4 are under 15·84, in the operated eye 7 are under 15·84.

is to be assumed from a scrutiny of the table given above. When degeneration of the ganglion cells took place the first to disappear were the smallest cells. These cells were not always distinguishable from the other cells of the ganglion and nerve-fibre layer, and even from small inflammatory cells (lymphocytes), so that in the early cases one may find somewhat conflicting results—*e.g.*, in Experiment IV. in which an increase in cells was obtained. This increase may be explained

by the fact that the region of retina examined in the operated eye was not strictly analogous to that of the control. In the later cases where there was less probability of the presence of inflammatory cells, whatever error there might be in the inclusion of extraneous cells was lessened, but always one was inclined to make one's enumeration somewhat larger than the actual, owing to the difficulty of differentiating degenerated ganglion cells from small neuroglial nuclei and lymphocytes.

In the case of the control, however, such confusion was not met with, since the ganglion cells were better defined and more easily distinguished. In this way the numerical results may be taken as somewhat *under-estimated*, so that the reduction obtained in the retina of the operated eye was even more substantial than it appears.

Thus we see that as early as forty-eight hours after operation certain changes in the ganglion cells were to be recognized. These changes consisted in a loss of perfect definition in the chromatin granules, probably due to the fact that the ground substance of the cell had taken up the stain to a slight extent. Degeneration apparently did not progress with extreme rapidity, the condition not being much more pronounced at eight days than at forty-eight hours. This is of significance when compared with the early chromatolytic changes described by Nissl and others, in case of peripheral nerve section. At three weeks, however, degeneration was definite and became more pronounced with the lapse of time, till at thirty-eight weeks (the longest time allowed) degeneration was practically complete.

Owing to the large range of variability shown by the retinal ganglion cells in the control eyes, one is diffident about drawing conclusions regarding the significance of the so-called "phenomena of degeneration." Adopting, however, as normal the appearances which in the control occurred with the greatest frequency, one endeavours to estimate not only the frequency with which the frankly abnormal types occur in the operated eye, but also (which is of more importance) to determine whether or not it contains "normal" cells.

Degeneration apparently attacks the medium and small cells at an early stage, and my observations were throughout the investigation chiefly confined to the largest ganglion cells. The smaller cells are especially liable to accident in the course of histological preparation, and are frequently of abnormal appearance even in the control. In any case, one must neglect the condition obtaining in the smaller cells, as there is difficulty in recognizing the gradual changes in any but the

largest ganglion cells. The type of normal cell, therefore, with which one makes comparison is the large multipolar ganglion cell in which the Nissl granules of various sizes are sharply stained, and are arranged in somewhat concentric rows around the more or less central nucleus. The nucleus contains numerous chromatin granules and one or more nucleoli. The ground substance of the cell body is unstained. Granules of chromatin are to be found for a considerable distance along the protoplasmic processes, and vacuoles may or may not occur. With regard to the occurrence of vacuoles, Birch-Hirschfeld emphasizes the fact, that in his cases vacuolation was confined entirely to the operated eye. In the present series, vacuolation was never more conspicuous in the cells of the operated than in those of the control eye—in many cases less so.

In recapitulating, therefore, one finds as the result of optic nerve section, that degeneration has set in as early as forty-eight hours, and is evidenced by the absence of entirely normal ganglion cells. Degeneration advances steadily and is estimated by the complete absence of normal cells, as well as by the progressive increase in the number of frankly abnormal or degenerated cells. At a period of thirty-eight weeks almost all the cells are atrophic.

Passing from the above degeneration of the sensory neurone of the higher or second order, one comes to a consideration of the fate of the more peripheral and independent neurones of the first order situated in the outer retinal layers. Judging from all authoritative accounts, the neurones of the retinal layers are in intimate relationship with one another. Birch-Hirschfeld described well-marked changes in the nuclear layers, as result of optic nerve section. These changes consisted, in the case of the inner nuclear layer, of reduction in size, irregularity of outline of the cell, and condensation of chromatin. The cells of the outer nuclear layer showed rounding of cells, reduction in the size of the interspace tending to obliteration of the "cross-striping," and loss of chromatin of edges ("cog-wheel" markings).

In the present series no essential changes in these layers could be made out. In some cases pale staining of the inner nuclei, or dense staining of the outer nuclei with slight loss of definition might be described, but these conditions are manifest in the control with so much frequency that their occurrence often appears to be due to differences of intensity of stain, rather than to pathological factors. In fact, one is often able to demonstrate from one slide in the control differences of staining which, if they were to occur in the operated eye, might be looked upon

as significant. The fact, however, that Birch-Hirschfeld mounted the corresponding sections from the two eyes upon the same slides probably eliminated error in this direction to a large extent.

More positive features than differences of staining power are those of *reduction in size, irregularity of outline*, and *loss of the discrete nature of the chromatin granules*. In the present series practically no evidence of such changes in the outer neurones was to be made out. One may, therefore, assume with fair confidence that the integrity of the outer neurones in these experiments has been preserved, and that the operation of section of their axon which produced serious damage in the case of the higher neurone (connecting the organ with central nervous system) was accomplished by little or no disturbance of the contiguous peripheral neurones. The slight loss of definition met with in the outer neurones in Experiment XI is compensated for by the absence of this feature in Experiment XIII (a much later period).

Having thus established the point that the peripheral neurones remain intact for such prolonged periods after separation from the central neurones, the question arises whether they are *intrinsically* more resistant than the outer neurones. To determine this, it was decided to study the progress of *post-mortem* changes in the retinal neurones.

B. Results of Autolytic Experiments.

(i) General Remarks.

Most of the previous work done upon *post-mortem* changes in nerve-cells has been concerned with the *post-mortem* changes in ganglion cells of the brain and cord. In the following experiments the changes occurring in the retinal neurones were investigated.

Birch-Hirschfeld [8] described *post-mortem* changes in the ganglion cells of the retina. He used the sublimate-thionin method and found evidence of change as early as two hours after death. There was slight folding of the nuclear membrane and loss of definition in the Nissl granules. The outer nuclear layer showed rounding off of the nuclei, especially of the rods, with commencing loss of "cross-striping" and edge crenation. After three and a half hours the ganglion cells showed enlarged vacuoles, especially at the periphery of the cell. The chromatin was still more or less in the form of granules. The nuclei of the internal nuclear layer were partially degenerated. There was no evidence of "cross-striping" in the nuclei of the external nuclear

layer. After five hours there was deep staining of the ground substance with blurring of the nuclear and cell-outline. After seven hours the Nissl granules had disappeared and the ground substance no longer stained deeply. The nucleus had practically vanished. The outer nuclear layer showed rounding of its nuclei with here and there a hint of "cross-striping." After eighteen hours the changes had progressed further and little or no chromophilic substance remained.

In the foregoing experiments it is not clear whether some of the changes described were not due to putrefactive conditions. In the present series, in order to eliminate as far as possible the influence of micro-organisms occurring in the surroundings, the following method of examination was adopted. The enucleated eyeball having been thoroughly cleared of all extrinsic structures (muscles, fat, &c.), so that a smooth contour might be obtained, the shortened stump of the optic nerve was grasped in forceps and the eyeball was plunged into melted paraffin (52° C.) for a few seconds. The thin layer of paraffin which adhered to the surface of the eyeball rapidly congealed, and the naked nerve was easily covered by a drop of paraffin poured on its surface. In this way the eyeball was sealed from the atmosphere by a layer of sterile material. The changes, therefore, which would take place within the eyeball were presumably those of *autolysis* and not *putrefaction*. The "enveloped" eyes were allowed to stand at room temperature (or in one or two cases at incubator temperature) for the desired period. When this had elapsed the layer of paraffin was easily chipped off and the eyeball treated henceforth in the same manner as the control. In the cases in which ox-eyes were used, the eyeballs were obtained from the slaughter-house with as little delay as possible, and could be looked upon for all practical purposes as fresh. In the case of the other animals (dog, cat, rabbit) the eyes were obtained in the laboratory and fixation took place immediately after the death of the animal.

(*ii*) *Experimental Details.*

Experiment 1.—Ox-eye. Autolysis for sixteen hours at room temperature. Fixation in picro-formol solution (a fixative which was successful in the case of the ox-eye although less satisfactory in the delicate rabbit retina).

Sections stained by Weigert's iron-hæmatoxylin method showed much disorganization of the rods and cones. The "palisade" arrangement of this layer was almost unrecognizable. Under low

magnification the other layers of the retina appeared unchanged when compared with the control. The external and internal nuclear layers were intact and separated from one another by the outer plexiform layer (which was of apparently normal thickness). Under higher magnification the cells of the external nuclear layer were seen to be densely stained and somewhat smaller than normal. The "cog-wheel" arrangement (Nissl staining) was still recognizable. The cells of the internal nuclear layer showed a reticulum in the form of more or less radiating strands around the deeply stained central nucleolus, and were on the whole slightly less sharply defined than in the control. The innermost cells of this layer ("centrifugal cells") with their downward passing processes were somewhat densely stained and stood out in strong contrast to the more feebly stained cells in the rest of the layer. The cells of the ganglionic layer were tolerably well preserved. Their processes stood out distinctly and the nuclear reticulum was well defined.

There was some blurring of the edges of the chromatin granules of the ganglion cells when stained with toluidin blue. The fibres of Müller stood out distinctly both as regards their nuclei and their fibrous expansions in the nerve-fibre layer.

Taken as a whole the changes which occurred in the ox-eye as the result of autolysis for sixteen hours are not fairly marked and resolve themselves into:—

(1) Disorganization of the rods and cones.

(2) Slight reduction in size of the rod and cone nuclei with a tendency to diffuseness of staining, although the "cog-wheel" appearance was still manifest.

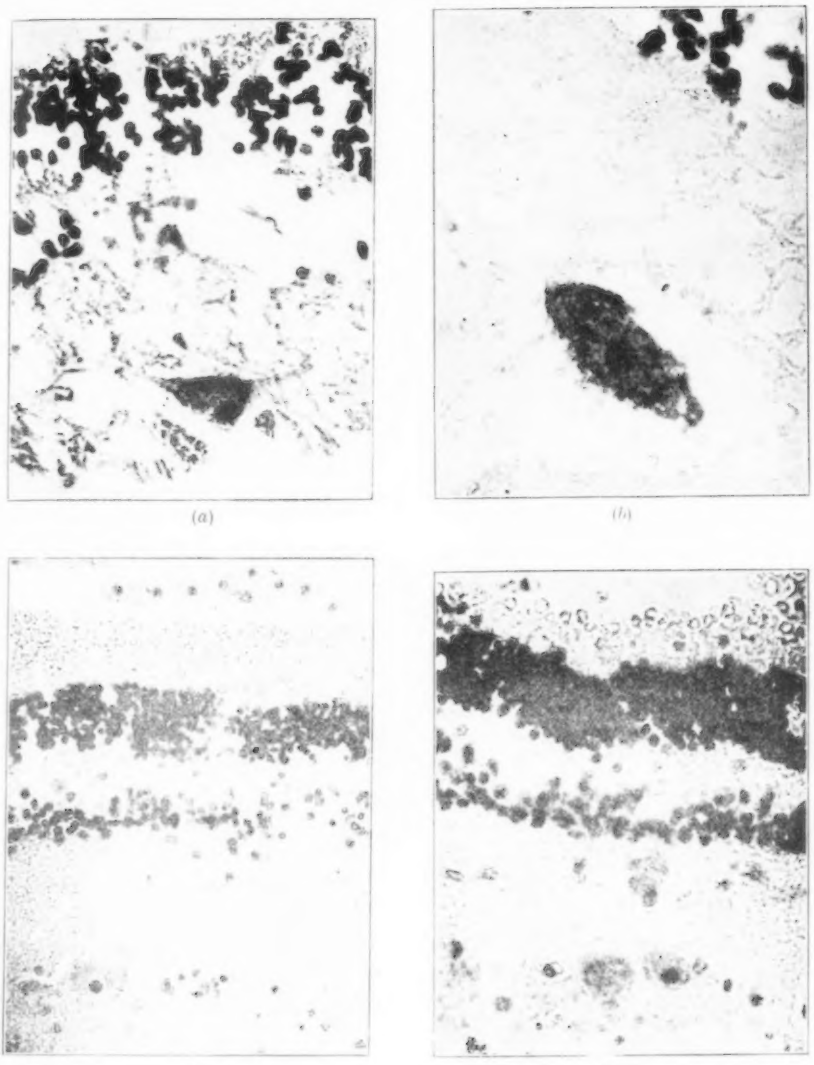
(3) Slight loss of prominence in the cells of the internal nuclear layer, with prominence of Müller's fibres and the centrifugal cells of the layer.

(4) Slightly increased prominence of the protoplasmic expansions of the ganglion cells which are thrown into relief by the commencing disorganization of the ground substance of the retina.

Experiment II (fig. 10).—Ox-eye. Autolysis for twenty-four hours (room temperature).

A. Fixation in 50 per cent. alcohol. Staining by Weigert's iron-hæmatoxylin and toluidin blue.

Under a low power the layers of the retina still appeared separate from one another. Under higher magnification the rods and cones were distinctly disorganized although a "palisade" formation was



(*a*) (*b*)

(*c*) (*d*)

FIG. 10.—Ox eye, autolysis twenty-four hours (room temperature).

(*a*) *Autolytic eye.* Fixation in 50 per cent. alcohol. Haemalum and eosin. Photomic. × 700. Large ganglion cell showing granular condition of the chromatin. The nucleus is somewhat eccentric. The protoplasmic processes are prominent. The cells of the external and internal nuclear layers are considerably more degenerated than the ganglion cells.

(*b*) *Autolytic eye.* Fixation in 50 per cent. alcohol. Tol. B. Photomic. × 1,000. Large ganglion cell with slight erosion of the cell margin. There is still a fair degree of granular differentiation, but the staining tends to be more diffuse than in control. The nucleus is deeply stained and is central. Protoplasmic processes not indicated.

(*c*) *Autolytic eye.* Fixation in $HgCl_2$. Haemalum and eosin. Photomic. × 500. The nuclear layers are still separated from each other by the outer plexiform layer. The cells of the nuclear layers are shrunken and densely stained. The ganglion cell to the left and below is somewhat ghost-like. The rods and cones have lost their "palisade" structure.

(*d*) *Autolytic eye.* Fixation in $HgCl_2$. Tol. B. Photomic. × 700. Note the dense staining in the somewhat shrunken cells of the outer and inner nuclear layers. The ganglion cells tend to become diffusely stained.

still suggested. The nuclei of the external nuclear layer showed a fair amount of detail, but there was a tendency to blurring of the edges and loss of "cog-wheel" marking.

The internal nuclei showed a well-defined chromatin network, but there was a tendency to enlargement of the spaces between the threads and a general "rarefaction." Many of these spaces appeared full of fat. The nuclei of Müller's fibres were deeply stained. The ganglion cells, both in the iron-hæmatoxylin and toluidin blue preparations, showed commencing degeneration. There was erosion of the inner aspect of the cell, and clear fat-like bodies could be discovered in many. There was a tendency to diffuseness of staining, and the Nissl granules had commenced to coalesce. The processes were not so well marked as in Experiment I (picro-formol fixation).

B. In another specimen fixed (i) by $HgCl_2$ (sat. sol.) and stained by toluidin blue, practically the same appearances were obtained, viz.: the ganglion cells were pale, and showed eroded inner margins; the cell processes were not well defined; the nuclei were well preserved; the outer and inner nuclear layers were not much changed; the rods and cones, however, were much disorganized.

(ii) In the part of the same retina fixed in 50 per cent. alcohol the ganglion cells showed rather more shrinkage and diffuse staining than existed in (i). The external and internal nuclear layers were approximated owing to the collapse of the outer plexiform layer, and the cells of these layers showed diffuse staining.

The discrepancy which exists between B. (ii) and A. may be explained by the fact that in the former a somewhat longer interval had elapsed before the eye was transferred to the laboratory, and that *post-mortem* changes had already set in. The difference between B. (i) and B. (ii) probably lies in the fact that, whilst fixation in the one case was procured by means of $HgCl_2$, in the other it was by alcohol. The latter reagent, in our experience, is the most satisfactory fixative for the Nissl method in fresh tissue, but in the autolytic retina, where the ground substance is unduly fragile and liable to shrinkage, the unfavourable effect of alcohol as a fixative is more pronounced than is the case in fresh, resistant tissues.

C. Another example of autolysis after twenty-four hours showed still more pronounced changes in the outer layers—the differentiation between the outer and inner nuclear layers having become lost owing to the almost complete disappearance of the outer plexiform layer. The ganglionic cells, however, exhibited practically the same features as in the other specimens.

Experiment III (fig. 11). — Ox-eye. Forty-eight hours (room temperature). Fixation in picro-formol solution. Staining in toluidin blue.

In the autolytic retina the layers were seen to be well differentiated, the plexiform layers being still recognizable. The layers of rods and cones, however, were entirely devoid of palisade structure. The external nuclei were densely stained, but there was still indication of the chromatin network ("cog-wheel"). The cells of the internal nuclear layer also were deeply stained, and the details of structure were much more obscure than in the corresponding cells of the control. The ganglion cells showed well-defined, diffusely stained processes,

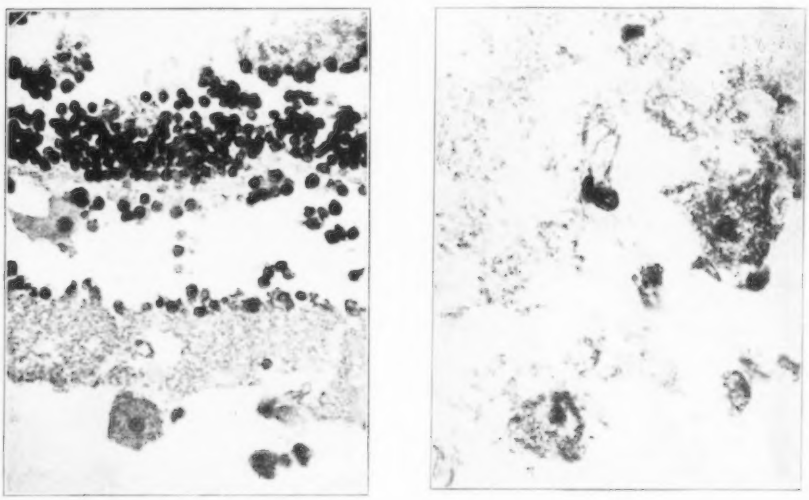
FIG. 11.—Ox-eye. Autolysis forty-eight hours (room temperature).

Autolytic eye. Fixation in picro-formol. Tol. B. Photomic. × 1,000. Large ganglion cell with conspicuous processes and well defined Nissl granules. Nucleus and nucleolus still well preserved.

which stood out against the surrounding tissue. The Nissl granules which were to be observed in the control were sometimes scarcely indicated in the autolytic retina, their place being taken by diffusely stained cell-contents.

Preservation of the ganglion cells in this specimen was on the whole little inferior to that in Experiment II, a fact which showed that autolysis, even after forty-eight hours, had produced marvellously little change in the ganglion cells.

Experiment IV.—Ox-eye. Autolysis for twenty-four hours at 37° C. The "enveloped" eye was placed in the incubator for twenty-four hours, after which fixation was carried out (at room temperature) in picro-formol solution. The control was left in picro-formol for twenty-four hours in the incubator, after which it was treated at room temperature. Staining was by Weigert's iron-hæmatoxylin method. In the control, by the picro-formol method, the rods and cones are well defined. The external nuclear layer showed the usual chromatin reticulum



(*a*) (*b*)

FIG. 12.—Ox-eye. Autolysis seventy-two hours (room temperature).

(*a*) *Autolytic eye.* Fixation in Müller's solution. Weigert's iron hæmatoxylin. Photomic. 500. The external plexiform layer is almost obliterated. The cells of the outer and inner nuclear layers are degenerated (shrunken, densely stained). Large ganglion cell at lower part of field shows somewhat eroded edges and densely stained nucleus.

(*b*) *Autolytic eye.* Fixation in 50 per cent. alcohol. Hæmalum and eosin. Photomic. 1,000. Ganglion cells with erosion of cell margins, but otherwise fairly well preserved.

("cog-wheel," &c.). The nuclei and processes of the ganglion cells were well stained, and the retinal vessels with their capillaries passing obliquely across the inner layers were particularly well demonstrated.

In the autolytic retina the rods and cones as such were no longer recognizable. The external nuclear layer was very much broken in outline, encroaching frequently upon the internal nuclear layer. The cells of the former were very deeply stained, and exhibited practically no

detail of structure. They were small and globular, and the "cog-wheel" marking was absent. The internal nuclei showed a fair amount of structural detail, but were considerably less well preserved than those of the control. The ganglion cells showed erosion of their inner edges. The nuclei were densely stained, and there was a general tendency to deposition of fat in the form of fine globules. The cell processes were conspicuous. Müller's fibres were reduced to the form of granular masses, their nuclei being densely stained and devoid of detail.

Thus we find in this experiment that subjection to heat has hastened the process of autolysis to a certain extent. The condition of the supporting structures is as much advanced as is the case in autolysis for forty-eight hours at atmosphere temperature (as evinced by the condition of Müller's fibres), and the degeneration of the nerve-elements is likewise much in advance of the condition found in autolysis for twenty-four hours at the lower temperature.

Experiment V (fig. 12).—Ox-eye. Autolysis for seventy-two hours at room temperature.

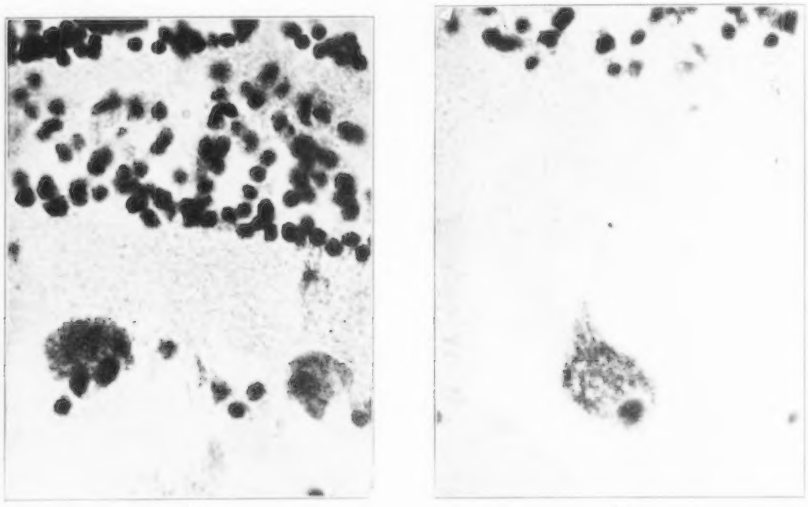
Fixation in Müller's fluid. No control preparation. The rods and cones were reduced to an amorphous *débris*. The retinal elements were fairly well differentiated into layers, but there was encroachment of the external nuclear layer inwards at places. The nuclei of this layer being circular, small and densely stained, were devoid of all detail ("cog-wheel," &c.).

The cells of the internal nuclear layer were not well differentiated, only here and there exhibiting an indication of the usual chromatin network. The nuclei of the blood capillaries were to be seen at places throughout the inner layers. The nerve-fibre layers showed some traces of fibrous structure. The ganglion cells had resisted and exhibited very fair nuclear structure. (The granules of the cell body were not brought out well by the fixative.) Vacuolation (? fat-globules) was present in many of the cells. Müller's fibres were scarcely visible.

Experiment VI (fig. 13).—Ox-eye. Autolysis for ninety hours at room temperature. Fixation in 5 per cent. alcohol. Stained by toluidin blue, and by hæmalum and eosin.

The external and internal nuclear layers were more or less fused together, and the normal stratification of the retina was often lost to view. It was not always easy to determine the layer to which the various cells belonged, since the cells of the nuclear layer had lost all internal detail, and appeared merely as small round spherical homogeneous bodies. The ganglion cells were still recognizable, and under

low magnification appeared to show fairly good preservation. They were, however, more rounded in outline than normal, the processes having almost entirely disappeared. The nuclei were often eccentric and were densely stained. Under high power the ganglion cells were seen to contain numerous fat-globules, the whole cell having a "stippled" appearance. There was occasional evidence of Nissl granules, but these bodies, when present, were blurred and washed out at the edges. Occasionally a long distorted dendritic process was seen in the degener-



(*a*) (*b*)

FIG. 13.—Ox-eye. Autolysis ninety hours (room temperature).

(*a*) *Autolytic eye.* Fixation in 50 per cent. alcohol. Tol. B. Photomic. × 1,000. Showing fusion of external and internal nuclear layers (the cells of the two layers are scarcely distinguishable from each other). Ganglion cells densely stained, but still showing indication of granules. The nuclei are deeply stained.

(*b*) *Control of* (*a*). Large ganglion cell with strong ap-going process. The nucleus is eccentric. Nissl granules lack perfect definition.

ated ground substance. Here and there one found a well-preserved nucleus showing the typical chromatin network, the cell body of which was almost absent. Erosion apparently always began on the inner aspect of the ganglion cell. The capillary framework was in many places particularly well demonstrated, the vessel walls apparently persisting for a considerable time.

In this experiment autolysis had been allowed to go on longer than

in any of the others. We find in it that collapse of the outer layers is almost complete; persistence of the innermost layers (ganglion and nerve-fibre layer) is marked. Degeneration of all the "supporting" tissue evidently occurred before that of the true nerve-elements, a point which emphasizes the differentiation between these structures. Degeneration occurred from the periphery of the cell inwards, the processes and cell body disappearing in many cases when the nucleus and central portion of the cell were tolerably intact. The cases in which the processes of the ganglion cells were conspicuous were to be explained by the fact that the ground substance being much degenerated, the comparatively resistant ganglion cells showed up with marked distinctness.

Experiment VII.—Rabbit-eye. Autolysis for eighteen hours at room temperature. Fixation in 5 per cent. alcohol. Stained with toluidin blue.

The rods and cones were no longer recognizable, having entirely lost their "palisade" arrangement. Müller's fibres were prominent. The cells of the external nuclear layer were densely stained, but often showed chromatin network ("cog-wheel" marking and "cross-striping"). The nuclei of the internal nuclear layer were "rarefied," the chromatin threads being attenuated and the interspaces enlarged. The ganglion cells showed well-marked Nissl granules, but there was a blotchiness of the granules, especially of those at the periphery of the cell. There was a ragged appearance of the cell margins, which was not—as was the case in the ox—chiefly confined to the inner aspect. The nuclei of the ganglion cells were somewhat densely stained, at others they were "rarefied," with only an indication of the normal structure. On the whole the retina was well preserved, as compared with the following two experiments.

Experiment VIII (fig. 14).—Rabbit-eye. Autolysis for twenty-four hours at room temperature. No control preparation of this experiment was kept. Fixation in 50 per cent. alcohol. Stained by toluidin blue and Weigert's iron-haematoxylin.

The rods and cones had practically disappeared. The fibres of Müller in their outer segments were almost invisible, but were well marked in the region of the nerve-fibre layer. The external nuclei showed slight evidence of cross-striping. The external plexiform layer was more or less collapsed, but showed occasional "cog-wheel" markings. The chains of chromatin, forming the network in the bipolar cells, were broken up, and the spaces between them enlarged so that the cells often

FIG. 14.—Rabbit-eye. Autolysis twenty-four hours (room temperature).

Tol. B. Photomic. × 1,000. Showing ghost-like ganglion cell with eroded edges. There is still evidence of the protoplasmic extensions. The nucleus is well preserved. Granular structure still visible in these cells.

FIG. 15.—Rabbit-eye. Autolysis forty-five hours (room temperature).

Fixation in 50 per cent. alcohol. Tol. B. Photomic. × 1,000. Large ganglion cell with well-preserved processes. The nucleus is central and is in a state of good preservation. Nissl granules are present, but there is a tendency to diffuse staining. The cells of the inner nuclear layer are degenerated, but less so than those of the outer nuclear layer.

appeared devoid of contents. The ganglion cells were much eroded at the edges and were rarefied. Their nuclei were generally fairly well preserved, but the cell bodies were fragmentary. Nissl granules were almost completely absent.

Experiment IX (fig. 15).—Rabbit-eye. Autolysis for forty-five hours at room temperature. Fixation in 50 per cent. alcohol. Stained in toluidin blue.

The retina had collapsed as a whole, and the portion available for examination was considerably reduced. The differentiation into layers at places was completely lost.

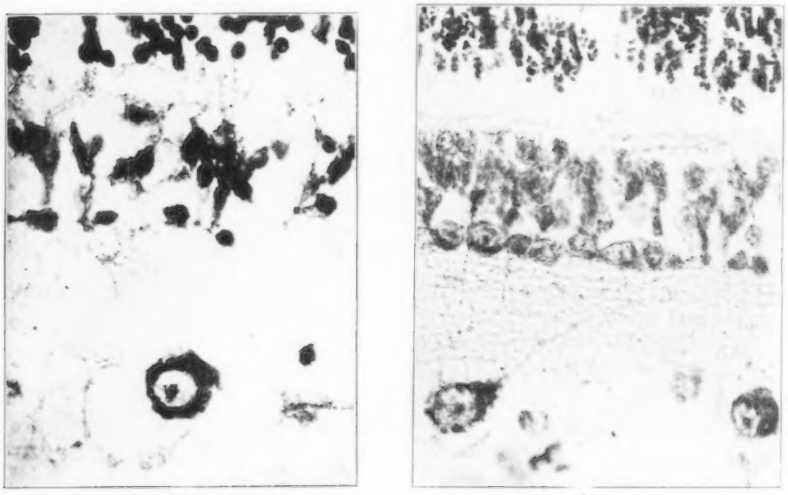
The nuclei of the external nuclear layer occasionally showed cross-striping, but there was no "cog-wheel" to indicate the network of chromatin. Müller's fibres were still more or less existent. There was a general tendency to diffuse staining in the cellular elements. The number of recognizable ganglion cells was small, their nuclei often being all that was left to mark their existence, and the cell body, if present, being much vacuolated. The processes were almost non-existent. The nerve-fibre layer was on the whole well preserved. Owing to the greater delicacy of the retina of the rabbit, the autolytic tissues were very liable to injury from histological manipulation. The finer gradations between the fresh condition and the more pronounced stages of autolysis were not demonstrable. As compared with the ox-eye, one observed that in the rabbit the fibres of Müller were more resistant, and the ganglion cells slightly less resistant.

Experiment X (fig. 16).—Kitten-eye. Autolysis for forty-eight hours at room temperature. Fixation in 50 per cent. alcohol. Stained by toluidin blue and by hæmalum and eosin. (This animal had been anæsthetized for several hours and the eyes were obtained about an hour after death.)

In the control we found that the rods and cones showed a slight fusion of their outer extremities. The nuclei of the external nuclear layer were arranged in many tiers (from four to six), the nuclei being elongated and rather densely stained. The chromatin network was very well demonstrated ("cog-wheel" and "cross-striping"). The internal nuclei were full of chromatin arranged in a fine network. The ganglion cells showed discrete well-stained Nissl granules arranged in concentric lines around the nucleus. The nucleolus was small and deeply stained. The processes of the ganglion cells were often very conspicuous. The blood capillaries were seen passing along the inner border of the outer plexiform layer, their endothelial nuclei being

sometimes difficult to distinguish from those of the horizontal cells of the internal nuclear layer.

In the autolytic retina there was considerable collapse of all the elements. The rods and cones were no longer visible. The nuclei of the external nuclear layer were represented by small, circular, densely stained masses of chromatin with almost complete loss of detail. The nuclei of the internal nuclear layer were devoid of cell body and showed only slight evidence of a chromatin nuclear network. The nuclei of Müller's fibres were often densely stained. The ganglion cells had



(*a*) (*b*)

Fig. 16.—Kitten-eye. Autolysis forty-eight hours (room temperature).

(*a*) *Autolytic eye.* Fixation in 50 per cent. alcohol. Tol. B. Photomic. × 1,000. Large ganglion cell with densely stained but still granular protoplasm. The nucleus is well preserved. The cells of the outer and inner nuclear layers are almost completely degenerated.

(*b*) *Control of* (*a*). Note the large typical ganglion cell with up-going process. The cells of the outer and inner nuclear layers present marked contrast to those of (*a*). Note the elongated rod nuclei with several horizontal interspaces between the chromatin masses.

as a rule, rounded outer margins and eroded inner margins. The protoplasm of the cell body had a "stippled" appearance. Nissl granules, when present, were blurred in outline. The nuclei of the ganglion cells often appeared practically normal, except for some wrinkling of the nuclear membrane. There was not much vacuolation in any of the cells. Certain cells appeared almost normal except for a slight loss in sharpness of detail.

Experiment XI.—Kitten-eye. Autolysis for ninety hours at room temperature. Fixation in 50 per cent. alcohol. Stained in toluidin blue, and hæmalum and eosin. (This animal had been the subject of a prolonged metabolic experiment.)

Control.—Hæmalum and eosin. The rods and cones were somewhat disorganized, and the external nuclei were densely stained, showing little internal detail, although a "cross-striping" was present.

The internal nuclei showed fair chromatin network in the hæmalum and eosin specimens. The ganglion cells showed vacuolation (fat-globules?) in many of the cells, even where there were typical appearances of Nissl granules and absence of diffuse staining. The edges of the cells, however, were often ragged and the processes were short. The small type of ganglion cell with eccentric nucleus and scanty protoplasm generally showed well-stained Nissl granules, although there was often a "washed-out" appearance of the chromatin which indicated that the cells were in a more or less abnormal condition.

In the *autolytic* eye the appearances were very different. The rods and cones were invisible as such, and the various layers of the retina had become fused. The external and internal nuclei under low power view were not to be distinguished from one another, both being represented by small, shrunken, densely stained spheres. Higher magnification did not reveal any differentiation of the chromatin into a network. No Müller's fibres were to be found, and the nuclei of these fibres were indistinguishable from the others of the internal nuclear layer. The ganglion cells were much reduced in number. When present they were seen as large, somewhat spherical, isolated cells, having a very finely granular, densely stained nucleus. The processes had disappeared. In some cells the inner margin had eroded (as in the ox-eye). Fat-globules occurred frequently, and Nissl granules were generally absent. The nearest approach to the normal consisted in a very finely granular condition of the cell protoplasm, with faintly outlined dendritic processes.

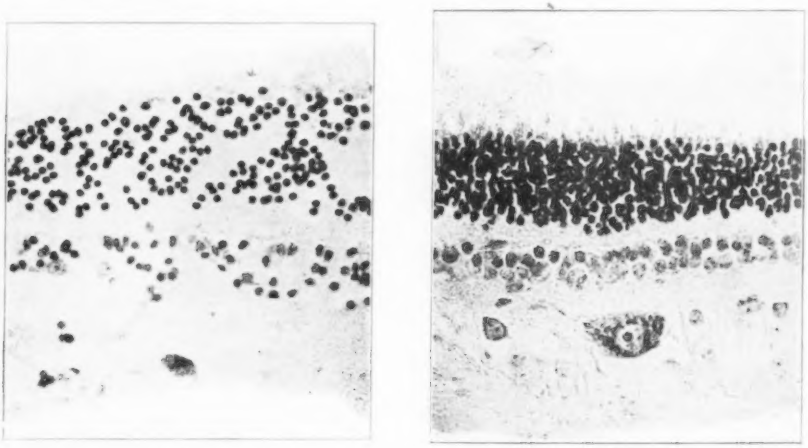
The preservation in this retina was on the whole much the same as that of the ox-eye for the same period of autolysis (Experiment VI).

Experiment XII (fig. 17).—Dog-eye. Autolysis for forty-six hours at room temperature. Fixation in 50 per cent alcohol. Stained by toluidin blue, thionin, and hæmalum and eosin.

Control.—The preparations stained by thionin showed fairly well defined Nissl granules, but there was slightly more staining of the ground substance than was the case in toluidin blue. In the latter the

granules stood out sharply defined against the colourless background. The protoplasmic processes of the ganglion cells were well differentiated in all the preparations. The nucleus was somewhat more densely stained by thionin than by toluidin blue. Vacuolation was, as a rule, absent. The blood capillaries were conspicuous as they crossed the internal nuclear layer to reach the external nuclear layer.

In the *autolytic* eye the rods and cones had become completely granular and unrecognizable as a palisade structure. The nuclear layers had become almost fused, the outer plexiform layer being greatly reduced in breadth. The external nuclei were densely stained and



(*a*) (*b*)

Fig. 17.—Dog-eye. Autolysis forty-six hours (room temperature).

(*a*) *Autolytic eye.* Fixation in 50 per cent. alcohol. Tol. B. Photomic. × 500. Showing degenerated cells of the outer and inner nuclear layers. These layers are still separated from each other by the outer plexiform layer. The large ganglion cell below shows erosion of the inner edges and diffuse staining of the protoplasm. Granular structure still recognizable.

(*b*) *Control of* (*a*). Note the large typical ganglion cell with well-marked Nissl granules, central nucleus, and up-going process. The cells of the outer and inner nuclear layers are well differentiated.

exhibited practically no structural detail (no "cog-wheel" or "cross-striping"). The "centrifugal" cells of the internal nuclear layer were fairly well preserved and showed considerable nuclear detail. The "horizontal" cells also were to be recognized. The ganglion cells showed erosion of the edges of the largest cells. The differentiation of the chromatin into granules was lost, the ground substance being

diffusely stained. The nuclei were often diffusely stained and lacking in detail. There was vacuolation, especially in the medium-sized cells. The cell processes were sometimes well preserved and stood out against the degenerated supporting elements.

On the whole, however, the ganglion cells in this specimen were well preserved, in many the presence of fairly typical Nissl granules being demonstrable. Erosion of the cells apparently began on the inner aspect, *i.e.*, at the side towards the axis-cylinder, although the nerve-fibres themselves were comparatively resistant. It was the epithelial-like elements of the retina (rods and cones) which perished early, the more strictly nervous structures (nerve-fibres, ganglion cells) being preserved for a considerable time. The delicate terminals, however, of the external plexiform layer early succumbed, allowing of fusion of the nuclear layers.

The principal points to be noted in these experiments are erosion of the margin of the ganglion cell with diffuse staining of the protoplasm, absence of definite Nissl granules and degenerative changes in the nuclei. Shrivelling of the cells took place, and was probably the ultimate fate of all the cells, but one was struck with the absence of marked shrinking of the cells, when compared with the results of Birch-Hirschfeld and others, whose experiments were concerned frequently with a shorter period of *post-mortem* degeneration.

(*iii*) *Discussion of Results.*

It is evident from the foregoing description that the appearances in the retina which are associated with *post-mortem* changes are very different from those which occur as the result of operation during life. We have seen that the ganglion cells which, in the case of section of their axons, readily tend to degenerate, are comparatively resistant to *post-mortem* changes, cells which show tolerably good preservation being found at a period of ninety hours after death (in the case of the ox-eye), forty-six hours (in the case of the dog), and forty-five hours (in the case of the rabbit). In the outer layers, however, we find degeneration setting in with considerable rapidity in the direction of from without inwards. The rods and cones are the first of all the elements to degenerate, disappearing in the case of the ox before sixteen hours, and in the rabbit before eighteen hours, but in the dog only partially at forty-six hours. The nuclei of the rods and cones begin to show degenerative changes about the same time, and the nuclei of the inner nuclear layer somewhat later.

In the experiments described, the shorter periods given for each animal are those at or about which the first definite changes were made out. For example, in the case of the ox, where the changes for sixteen hours are defined, it is to be understood that changes may occur at a period less than that, but they are so slight and show so little progression that one has not placed undue importance on their recurrence. The lapse of several hours seemed to produce little effect on the cells when the eye was sealed from the atmosphere, and one's object was not so much to set a time limit upon the onset of changes as to investigate their sequence in the various layers. In the case of the rabbit retina it is true that changes set in before eighteen hours, but they are not pronounced, and one selected the periods at which definite changes are to be observed.

In the series described by Birch-Hirschfeld, changes are met with in all the elements as early as two hours after death, ending in complete destruction at eighteen hours. The difference between such results and those of the present series in which well-preserved ganglion cells are met with at a period of forty-five hours is probably accounted for by the fact that in the former case *putrefaction* was not excluded as a causal factor, whereas in the latter the possibility of its occurrence was reduced to a minimum.

Part III.—Conclusions.

(1) The range of variability amongst the so-called normal ganglion cells of the retina is considerable, and the differences are so great as to lead to the conclusion that the features described under the term *chromatolysis* are not necessarily pathological.

(2) The smaller ganglion cells of the retina seem to be specially liable to changes, and atypical cells are prevalent in the control experiments. They are to be discarded in the present investigation. The large multipolar cell, which in the healthy retina is of most frequent occurrence, appears recognizable as a type. This cell contains a central nucleus with one or more nucleoli, and shows, when treated by the alcohol-toluidin blue method, sharply defined Nissl granules of different sizes arranged more or less concentrically around the nucleus, the ground substance being quite colourless. Departure from this type to any marked extent may be taken to indicate abnormal changes.

(3) It is the absence of truly normal cells in any retina, rather than the occurrence of isolated abnormal cells that indicates a pathological

condition. When the number of normal cells is *nil*, and that of abnormal cells is excessive, degeneration is fairly established.

(4) The gradual sequence of chromolytic change (swelling of the cell body, eccentric position of the nucleus, diffuse staining of the protoplasm, vacuolation, &c.) is not demonstrated by the retinal ganglion cells. One is not always able to demonstrate the changes between the first trace of degeneration in a cell (loss of definition in the Nissl granule), and complete atrophy. Almost normal cells may be found side by side with others in which there is diffuse staining of the protoplasm and nucleus, or others in which the cell is pale and contains small dust-like particles. Degeneration of any cell is indicated by the early loss of definition in Nissl granules and by the final or atrophic stage of the cell-process. Vacuolation is met with in the control with at least as much frequency as in the operated eye and probably does not represent the existence of a pathological condition during life.

(5) As a result of section of the optic nerve, the fibres of which constitute the axons of the ganglion cells of the retina, degeneration of the ganglion cells sets in as early as forty-eight hours after operation. Degeneration advances with the lapse of time, is pronounced at three weeks, and is complete at thirty-eight weeks, where all the cells are atrophic. The ganglion cells are the central sensory neurones of the retina, and are seen thus to perish upon section of their central processes.

(6) Practically no change takes place in the cells of the outer and inner nuclear layers, *i.e.*, in the more peripherally situated neurones existing in contiguity with the ganglion cells. They are therefore seen to remain unchanged when their connexion with the central neurones is severed. As peripheral neurones they are thus seen to have an independent existence.

(7) The fact that these peripheral retinal neurones have no special power of resistance is illustrated by the series of autolytic experiments in which degeneration was seen to occur in the reverse order from that of the optic nerve section experiments. The layer of rods and cones with their nuclei degenerate first, the inner nuclei being next to perish, the ganglion cells being comparatively resistant.

In conclusion, I wish to record my sense of great indebtednesss to Professor D. Noël Paton, under whose constant supervision this work has been carried out; also to Dr. G. Herbert Clark of this Laboratory for assistance in the operations.

The photomicrographs were taken by Mr. Richard Muir, Edinburgh. The camera lucida drawings are my own work.

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PLATE I.

Experiment II. Forty-eight hours after section of the optic nerve.

(1) *Operated.* Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Ganglion cells selected from different fields to show the best preservation. Note diffuse staining in most of the cells. The cells are smaller than in (2).

(2) *Control.* Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Different types of ganglion cells which occur normally. (*a*) is a so-called "normal" cell; (*b*) is a rarefied or "ghost" cell; (*c*) shows the nucleus eccentric.

Experiment V. Four days after section of the optic nerve.

(3) *Operated.* Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Showing ganglion cells from different fields. Most of the cells are small and stain feebly. The chromatin granules are dust-like. No quite normal cells appear (compare control).

(4) *Control.* Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Ganglion cells from different fields. (*a*) normal" cell; (*b*) small cell with eccentric nucleus and peripherally situated granules.

Experiment VII. Eight days after section of the optic nerve.

(5) *Operated.* Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Ganglion cells selected from different fields. Note pale staining and dust-like condition of the Nissl granules.

(6) *Control* as in (5) ganglion cells from different fields illustrating various types of cell, some of which are not "normal." Normal cells are frequent in the sections, however.

Experiment IX. Three weeks after section of the optic nerve.

(7) *Operated.* Fixation 50 per cent. alcohol. Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Showing small diffusely stained ganglion cells. The larger cells seen to the left show a dust-like condition of the chromatin.

(8) *Control* as in (7). Showing sharply defined Nissl granules in the ganglion cells.

(9) *Operated.* Fixation in $HgCl_2$. Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Ganglion cells from different fields. The cells are smaller than in control and have greater tendency to diffuse staining. No "normal" cells are to be found.

PLATE II.

(10) *Control* as in (9). Ganglion cells from different fields. These cells illustrate the atypical cells often met with in the controls.

(11) *Operated.* Fixation in formol saline. Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Ganglion cells showing somewhat diffuse staining. Vacuoles are frequent. The cells are smaller than in (12).

(12) *Control* as in (11). Ganglion cells showing large Nissl granules. Vacuoles are met with.

Experiment X. Six weeks after section of the optic nerve.

(13) *Operated.* Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Note the much diminished ganglion cells as compared with control. Staining is diffuse or there is a dust-like condition of the granules. (*a*) represents the nearest approach to a "normal" cell.

(14) *Control* as in (13). Note large typical ganglion cells (*a*) and (*b*), with atypical forms (*c*) and (*d*).

Experiment XI. Fifteen weeks after section of the optic nerve.

(15) *Operated.* Fixation in formol saline. Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Showing ganglion cells much diminished in size. Diffuse intense staining is the rule. There is no vacuolation. Pericellular spaces not enlarged. No normal cells are to be found.

(16) *Control* as in (15). Ganglion cells from different fields. Note vacuolation in (*a*), enlarged pericellular space in (*b*).

(17) *Operated.* Fixation in 50 per cent. alcohol. Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Ganglion cells from different fields. Note small size of cells, diffuse staining and absence of vacuolation. Pericellular spaces occasionally seen (*a*).

(18) *Control* as in (17). Showing many normal ganglion cells (*a*), with others (*b*) less typical.

(19) *Operated.* Fixation in $HgCl_2$. Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Showing differentiation even less well marked than in (17).

(20) *Control* as in (19). Differentiation less pronounced than in (19).

Experiment XII. Sixteen and a half weeks after section of the optic nerve.

(21) *Operated.* Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Ganglion cells much diminished in size. The chromatin, when granular, is lightly stained and is in the form of fine dust-like particles. Usually, however, there is a condition of dense diffuse staining of the protoplasm.

PLATE III.

(22) *Control* as in (21). Ganglion cells show large well-defined Nissl granules. A few rarefied cells may be seen (*a*).

Experiment XIII. Thirty-eight weeks after section of the optic nerve.

(23) *Operated.* Fixation in $HgCl_2$. Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Ganglion cells from different fields. Note the small size and absence of well-defined Nissl granules. There is wrinkling of the nuclear membrane; pericellular spaces are not enlarged.

(24) *Control* as in (23). Shows various types of ganglion cell. In (*a*) there is diffuse staining. Note presence of large cells with well-defined Nissl granules, a type never found in (23).

(25) *Operated.* Fixation in formol saline. Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Illustrates the condition of atrophy in the ganglion cells. Note shrunken cells and lack of vacuolation. Pericellular spaces not enlarged. Diffuse staining is prevalent, practically no granular structure being indicated.

(26) *Control* as in (25). Ganglion cells from different fields, showing large well-defined granules. Note vacuoles and conspicuous pericellular spaces.

Ox-eye, autolysis twenty-four hours (room temperature).

(27) *Autolytic eye.* Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Ganglion cells selected from different fields. Note their well-preserved condition. The processes are often conspicuous. Granular structure is well marked. There is occasionally a tendency to pale staining and vacuolation.

PLATE I.

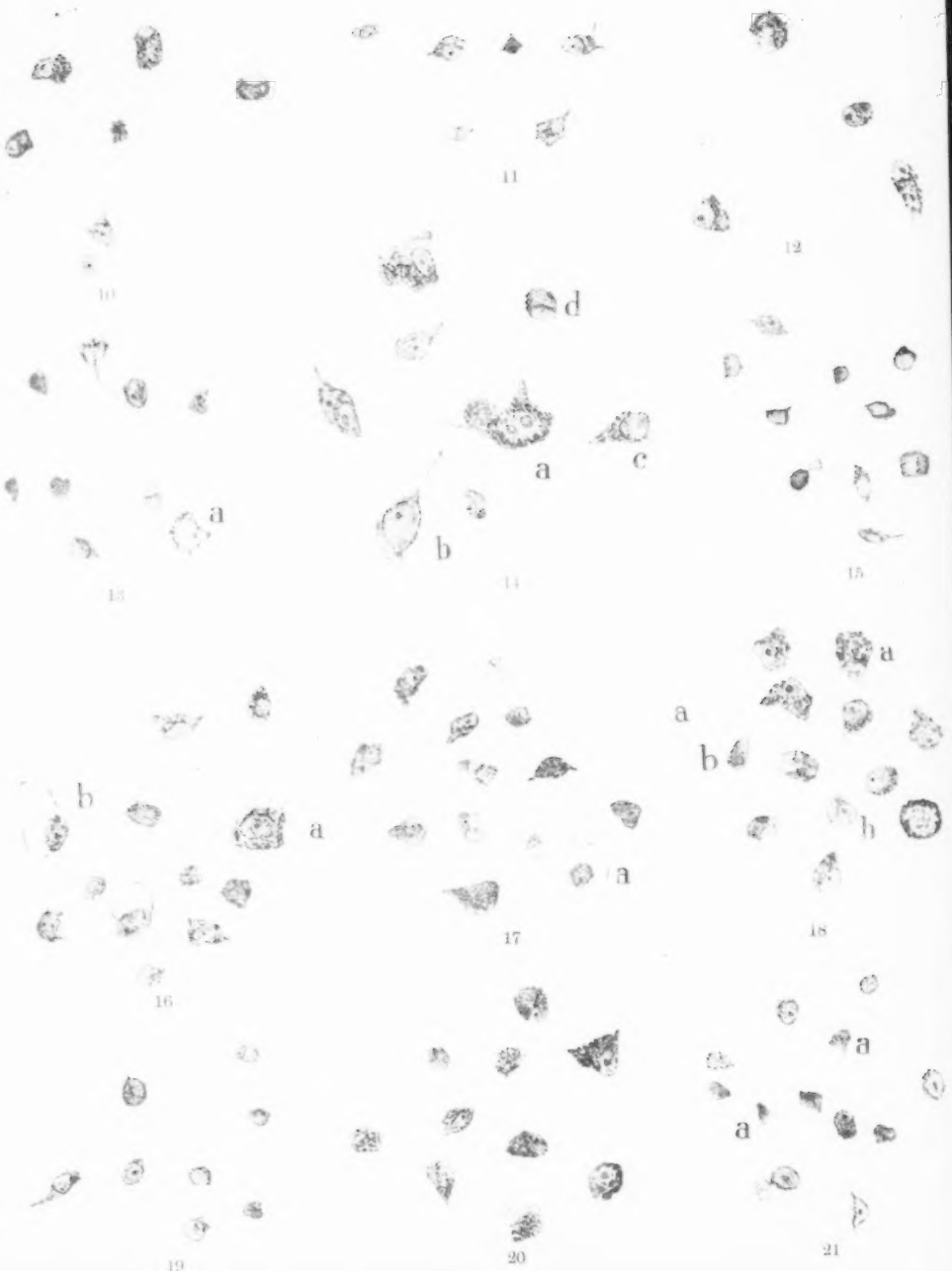

PLATE II.

(28) *Autolytic eye.* Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Ganglion cells selected from different fields. The smaller cells show rather diffuse staining. The larger cells are somewhat ghost-like.

(29) Same as (28).

(30) *Control.* Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Showing different types of normal cells. (*a*) rarefied cell with eccentric nucleus; (*b*) cell containing discrete Nissl granules and eccentric nucleus: (*c*) cell which is profusely vacuolated: (*d*) small cell diffusely stained.

PLATE IV.

Ox-eye. Autolysis ninety-hours (room temperature).

(31) *Autolytic eye.* Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Ganglion cells from different fields. Staining is somewhat diffuse and often intense. The cell margins are eroded. Protoplasmic processes generally wanting. There is still indication of granular structure.

Kitten's eye. Autolysis forty-eight hours (room temperature).

(32) *Autolytic eye.* Fixation in 50 per cent. alcohol. Drawing (c.l.), o.i., $\frac{1}{12}$. Ganglion cells from different fields. Note the well-preserved cell processes; in (*a*) the stain tends to be diffuse.

(33) *Control of* (32), showing ganglion cells from different fields. (*a*) typical cell; (*b*) rarefied or ghost-like cell; (*c*) cell with tendency to diffuse staining of the protaplasm.

Dog's eye. Autolysis forty-six hours (room temperature).

(34) *Autolytic eye.* Tol. B. Drawing (c.l.), o.i. $\frac{1}{12}$. Ganglion cells from different fields. In (*a*) there is profuse vacuolation, and the cell-margins are eroded; (*b*) cell with well-defined process; (*c*) almost normal cell, showing tendency to diffuseness of stain.

(35) *Control of* (34). Ganglion cells from different fields. (*a*) typical cell with well-defined Nissl granules, central nucleus, and well-marked process; (*b*) somewhat rarefied cell, with eroded margins.

TOXIC DEGENERATION OF LOWER MOTOR NEURONE CELLS COMMENCING DURING INTRA-UTERINE LIFE IN AN INFANT DYING AT 2½ MONTHS.

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THE following case is worthy of being placed on record, because it is a rare example of atrophic paralysis noticed in a child at birth, and contributing to its early death at the age of 2½ months.

C. D. was born on September 30, 1909. Delivery took place at full term and was normal in every respect. The father and mother were said to be healthy and the patient was the last of eleven children, the eldest of whom was 17 years of age. There had been one miscarriage in connexion with the first pregnancy, the second child was premature and only lived a few days, and another child died in convulsions at 9 weeks; in other respects the children were healthy. The mother stated that this child had never moved her legs since birth and that she had not moved her arms since she was three days old. She had never been able to move her head.

On November 26 the mother noticed the child was very thin about her chest and arms and took her to Guy's Hospital, where she continued to attend as an out-patient until December 17. The child had never been able to cough or to cry.

On December 17 the child was admitted to the Belgrave Hospital for Children under my care and I saw her at 9.45 p.m. She was pale and cold, with feeble pulse and subnormal temperature. She was fairly well nourished and had taken food satisfactorily until two days before admission. The bowels had acted naturally.

On examination I found her breathing rapidly, about 60 times a minute, and her pulse going at the rate of 150 beats per minute. The respiration was being carried on entirely by the diaphragm, which appeared to be acting vigorously. There was no sign of any intercostal movement, in fact the costal cartilages were drawn in on both sides of the sternum, from the first downwards, with the result that there was a remarkable degree of pigeon-breast. The accessory muscles of respiration were not employed, and there was slight recession of the intercostal spaces. The most striking feature in the child's appearance was the general flabbiness and lack of "back-bone." The face was

expressionless, the mouth hung open and the head fell loosely in response to gravity without any attempt at support on the part of the neck muscles. With the exception of the diaphragm and the extensors and flexors of the fingers, all the muscles of the trunk and arms appeared to be completely paralysed. The fingers were sustained in the claw position and there were occasional spontaneous movements of the fingers, generally in the direction of flexion.

The legs were also flaccid and never moved spontaneously. The stimulation of the soles of the feet gave rise to faint flexion of the ankles and of the knees. The eye movements appeared normal and I have no doubt that she

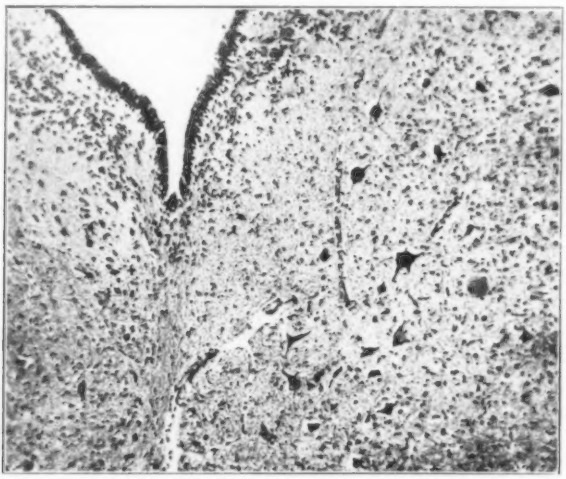

FIG. 1.—This photograph gives a general view of the hypoglossal nucleus and shows the scarcity of normal cells of good size and shape, as well as one or two which are undergoing chromatolysis.

both saw and heard. Swallowing was performed naturally but slowly. It was impossible to form any opinion about her sensibility to pain or touch. The abdominal reflexes were not obtained. No tendon-jerks were elicited and I could obtain no contraction of any muscles on direct percussion. The lungs were resonant all over, but scattered râles could be heard in many places. Examination of the heart revealed no definite disease.

The child died suddenly at 10.30 p.m.

Post-mortem, sixteen hours after death: Rigor mortis of a kind was present, that is to say, the whole of the soft tissues seemed to consist of a thick putty which could be easily moulded by the fingers and which bore the mark of every pressure.

Dense pale subcutaneous fat was abundant everywhere. The muscles were generally small but natural in colour.

The brain and spinal cord were natural in appearance at first sight. On closer examination the anterior roots of the cord and the lower cranial nerves, *i.e.*, seventh, tenth, eleventh and twelfth, looked small and fragile and were difficult to detect. The posterior roots and the third, fifth, sixth, and eighth nerves appeared to be of normal size and well myelinated compared to the others.

There was a large thymus reaching down to the diaphragm on the right side and nearly as far on the left, and attached above to the vessels behind the top of the sternum. It was natural in appearance.

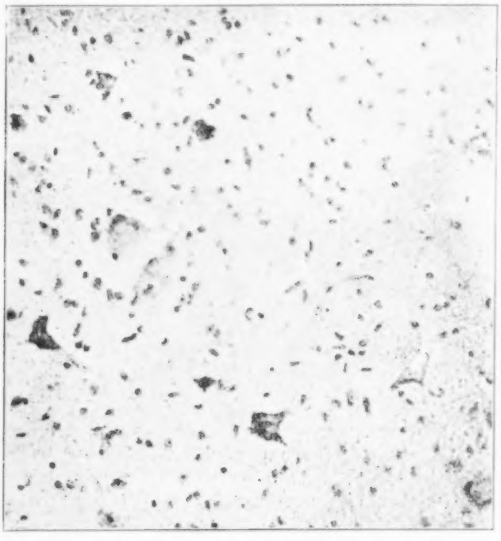

FIG. 2.—Cells of the hypoglossal nucleus, two of which are fairly healthy but poorly differentiated. Two others are of the "ghost" variety.

The thyroid gland looked natural. Below the thyroid on either side of the trachea were two or three large glands (? parathyroids). There were no signs of pressure on the trachea anywhere. The lungs were covered with petechial hæmorrhages and there was bronchitis and some basal congestion. Heart normal. Liver and spleen and kidneys normal. Well-developed suprarenals. Mesenteric glands large but not obviously diseased. Lymphatic elements in intestinal wall not conspicuous.

The nerves were natural in appearance. Portions of the ulnar, radial, median and sciatic were kept. Muscles were taken from the

neck, back and front, diaphragm, front of forearm and hamstring region.

Microscopical Examination.

Central nervous system. — Parts of the cerebral cortex, mesencephalon, medulla and spinal cord were examined by the Nissl method, the Weigert-Pal method, by the Marchi method, and by the Van Gieson stain.

The cerebral cortex showed nothing abnormal. Sections through the oculo-motor nuclei were also free from obvious changes. Sections

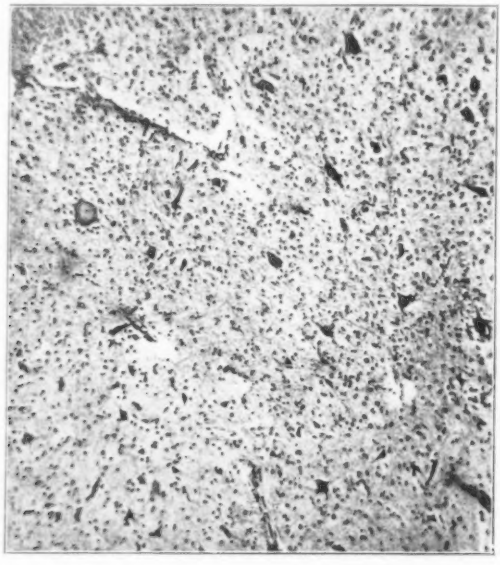

Fig. 3.—Anterior horn from the cervical region. Note the paucity of cells and their poor quality.

through the medulla showed marked changes in the cells of the hypoglossal nucleus. The number of cells was diminished and few of the cells which remained could be regarded as healthy. The majority were small and appeared to be generally atrophic; others presented swelling and marked chromatolysis. In the spinal cord the anterior grey matter at all levels showed similar changes in regard to the ganglion cells. The deficiency in number and the poor size and irregular shape of the survivors were noticeable everywhere. There were no signs of reaction

or inflammation in any part of the cord or brain-stem, and the vessels appeared to be perfectly healthy. Sections of the spinal cord stained by the Marchi method showed a few scattered degenerated fibres in the posterior columns at all levels, but no sign of degeneration in any other parts. In the Weigert-Pal sections the appearances were normal when the age of the child is taken into consideration.

Peripheral nerves.—The ulnar, radial, median and sciatic nerves were examined. By the Weigert-Pal method they appeared to be well myelinated. No interstitial changes were to be seen in sections stained by ordinary methods. By the Marchi method a very small number of

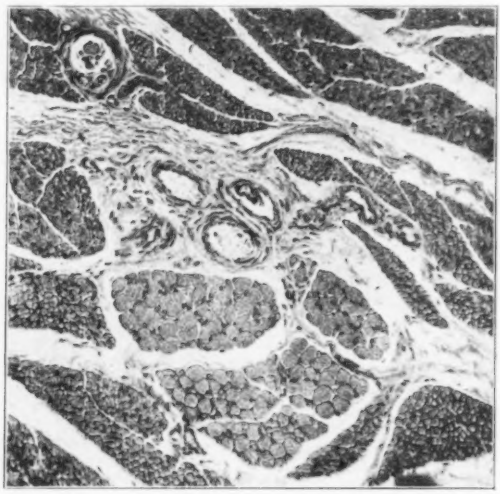

FIG. 4.—Transverse section of flexor muscle of forearm. Five bundles show a preponderance of fair-sized fibres; all the other bundles contain minute fibres.

fibres showed slight evidence of changes in the myelin sheaths, but these were insignificant as compared to the marked changes found in the anterior horn cells and in the muscles.

Skeletal muscles.—All the muscles examined showed similar changes varying in intensity. Both in transverse and longitudinal sections great differences could be seen in the condition of various bundles of fibres. Some appeared to be normal in size and in other respects: others showed varying degrees of simple atrophy, or, what might be another interpretation, of imperfect development. It was characteristic of these muscles that individual bundles were affected rather than individual

fibres, as will be seen in the accompanying photographs. There was no evidence of any interstitial change and the muscle-spindles presented a healthy appearance.

Other organs.—Microscopic examination of the heart, liver, spleen, suprarenals, thymus gland and mesenteric glands revealed no signs of disease.

A consideration of the clinical history and pathological examination of this unusual case leads to the conclusion that there must have been some toxic influence at work during the later period of intra-uterine life. It is justifiable to suppose that the poison affected chiefly the motor nuclei of the medulla and spinal cord, and so indirectly caused

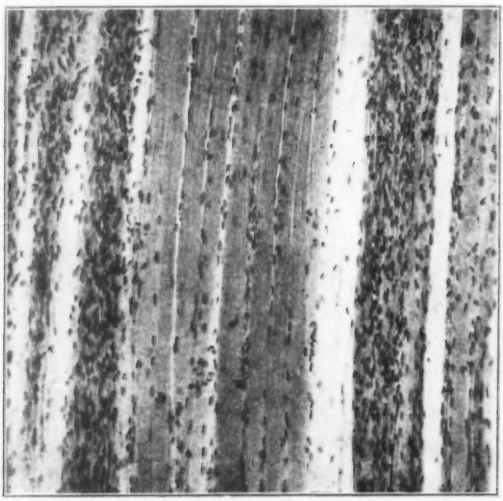

FIG. 5.—Longitudinal section from the same muscle.

degeneration of the muscle-fibres throughout the body, or interfered with their natural development. It is tempting to suggest that the small atrophic cells of the anterior horns and hypoglossal nuclei represent those which failed to develop, while the swollen "ghost cells" represent the few which reached maturity, only to fall victims to the circulating toxin. Such a theory might help to explain the relative paucity of fibres in the peripheral nerves, which were shown to be undergoing degenerative changes.

It is difficult to believe that any myopathic disease could be the primary morbid process in view of the changes found after death.

PATHOLOGICAL EXAMINATION OF THE FRESHLY FIXED EYES FROM A CASE OF AMAUROTIC FAMILY IDIOCY.

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In a case of amaurotic family idiocy recently reported in Brain (J. F. Poynton, J. H. Parsons, and G. Holmes [6]) the pathological examination of the eyes was admittedly incomplete, as they were only obtained thirty hours after death, and had suffered much from *post-mortem* change. The following case, in which the eyes were excised immediately after death and in which fixation left nothing to be desired, may serve to supply some missing details. For the notes of the patient's condition during her residence in hospital, and for the trouble taken to obtain the eyes, we are deeply indebted to Mr. Hildred Carlyll, Resident Medical Officer to the East London Hospital for Children.

Clinical Notes.

The patient, Jenny M., was the child of Russian Jews who were not related. She was the youngest of five children, of whom the first and third died in infancy, not of this disease: the second is now 8 years old and well; the fourth was an amaurotic idiot, and died at the East London Hospital for Children. This case was reported by Dr. F. W. Mott [8].

The present patient was brought to the hospital first when one month old, and again two months later, because the mother thought she was not observant. At the second visit the fundi were found to show the typical picture of amaurotic family idiocy, with partial optic atrophy. The patient was a full-time child; she was breast-fed for eleven months, and when 1¼ years of age was admitted as an in-patient.

On admission her weight was 1 st. 6 lb. She was fairly well nourished, ate

and slept well, and cried less than other children. Heart and lungs normal. No convulsions. Limbs spastic. The eyes were kept open, but she took no notice of external objects; the pupils were dilated, but reacted sluggishly to a strong light. No nystagmus or strabismus.

For four or five months nasal feeding was employed, but the child gradually went downhill and became more stuporose. The limbs were more spastic, the head retracted, and she lay as she was placed without offering to move. The forearms were pronated, the wrists flexed, the thumbs much adducted, and claw hand was present. Knee-joints flexed; very great drop foot. Sores gradually developed at the site of contractures; and at death were present to an extreme degree, as was also the muscular wasting. Extensor plantar reflex on each side. The optic atrophy became complete. Latterly several attacks of bronchitis occurred, with pyrexia, but for the greater part tempera-

FIG. 1.

General view of the macula. The foveal pit is shallower than normal owing to thinning of the ganglion cell and nerve-fibre layers on each side. All the other layers are strictly normal. In the ganglion cell layer large, round, swollen-looking cells occur; they sometimes lie in spaces which they do not completely fill. Many of the small dark nuclei also belong to ganglion cells; some are neuroglial.

ture was normal. Death occurred when the child was a little over 2 years of age. Permission having been previously obtained, the eyes were immediately enucleated and fixed, one in Zenker's fluid, one in Müller. Further than this, no *post-mortem* examination was allowed.

PATHOLOGICAL EXAMINATION.

Both eyes were divided horizontally immediately above the level of the macula. The halves containing the macula were embedded in celloidin, and a complete series was cut through that region, every section containing the foveal pit being mounted. Paraffin sections were made from the retina of the other half.

The stains used were hæmatoxylin and eosin, v. Lenhössek's modification of the Nissl method, and Mayou's modification of Pappenheim's stain [13],

which proved excellent for the study of the nucleolus and of the finer changes in the nucleus and protoplasm. Giemsa's stain was also used, but, beyond defining the cell bodies, rendered no special service. The Müller-fixed eye was stained by the Weigert-Pal process.

Probably owing to the methods of fixation, Bielschowsky's method did not yield satisfactory staining. By far the best results were obtained from the Zenker-fixed eye, in which the histological preservation, as judged by the state of the rods and cones, was practically perfect.

Microscopical Examination.

The changes are absolutely confined to the ganglion cells and their corresponding nerve-fibres. Owing to a certain diminution of these elements the foveal depression is shallower than normal; otherwise the general architecture of the macula is quite unchanged: there is no folding, œdema, or detachment, and the nuclear, reticular, and rod and cone layers are strictly normal (fig. 1).

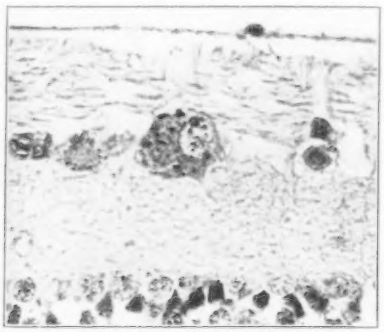

Fig. 2.

× 600. A normal ganglion cell, stained with Mayou's modification of Pappenheim's stain.

In reality, the loss of ganglion cells is not nearly so great as it seems, the appearance being due partly to the poor staining and inconspicuousness of the cell body, chiefly to the shrinkage of the nucleus: in the vicinity of the fovea, three to four layers of ganglion cells can usually be counted, the average in this situation being about five. Ganglion cells are found right out to the periphery of the retina, and in that situation seem to be, on the whole, less affected than in the macula. The ganglion cells which normally occur in the inner nuclear layer are also degenerate. The nerve-fibre layer is atrophied, but less completely so on the nasal than on the temporal side. The choroid beneath the macula and elsewhere is normal. The central vessels are normal, both in the nerve and in the retina.

The most striking change in the cell protoplasm is the total absence of Nissl granules. Not a single cell is to be found in which they are normal;

only exceptionally are they indicated at all by the presence of a rather coarsely granular material which takes on a purplish or violet tinge with thionin (fig. 4); for the most part all trace of them has disappeared.

In the cells which have undergone least change the normal cyto-reticulum is fairly well preserved, and the protoplasm is finely granular. Advancing

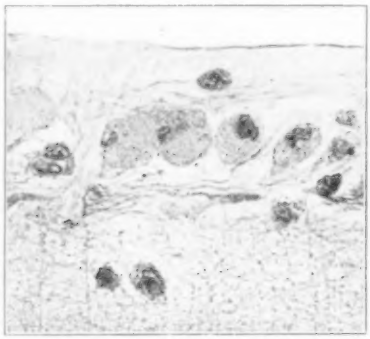

FIG. 3.

× 600. Ganglion cells from the present case, stained by the same method. The cells are round in shape, but not enlarged; the Nissl granules are lost. The protoplasm is finely granular, but one of the cells shows a large area in which it is homogeneous (and stained greenish). The nuclei are shrunken and crenated. The nucleolus is visible in the right hand cells.

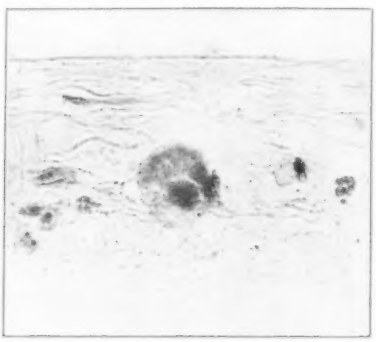

FIG. 4.

× 600. A ganglion cell, stained by v. Lenhössek's modification of the Nissl method. It is enlarged and filled with a granular material which stains purplish. This type of cell is very exceptional. All trace of the granules is usually lost.

degeneration is indicated by the appearance within the cell, usually near the nucleus, of a vacuole-like area filled with a perfectly homogeneous substance, the remains of the granular protoplasm being displaced to the periphery (figs. 3 and 4). With Mayou's modification of Pappenheim's stain this new

substance takes on a light greenish tinge which is quite foreign to the normal cell; in hæmatoxylin-eosin specimens it is slightly bluish. These homogeneous areas increase at the expense of the normal cytoplasm, and finally may replace it entirely: it is rare to find more than one area in a single cell, but sometimes there are several separated by a network of granular protoplasm. True vacuoles, without contents, are not found.

Only exceptionally is a cell found with any indication of the normal cell processes; for the most part they have completely disappeared. In consequence the cells have a more or less rounded shape, and this, together with the homogeneous nature of their contents, and the shrinkage of the nucleus, gives them a swollen, bloated appearance. Comparison with normal ganglion cells shows, however, that though there is considerable variation, the average size of the cells is, if anything, below rather than above the normal. True swelling is almost confined to the vicinity of the fovea, where some of the cells are greatly enlarged, have a perfectly homogeneous protoplasm, and lie within spaces which they do not completely fill (fig. 1).

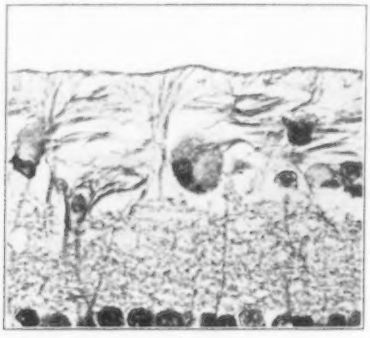

FIG. 5.

× 600. A ganglion cell stained with hæmatoxylin and eosin. It shows the rounded form, the eccentric nucleus, and the formation of a vacuole-like homogeneous area in the protoplasm.

Normal nuclei are scarcely to be found. The characteristic change is a shrinkage whereby the outline becomes crenated and the chromatin reticulum condensed. In the more degenerate cells the reticulum becomes indistinct, the nucleus being filled with irregularly disposed granules of varying degrees of coarseness. The ordinary nuclear stains are consequently taken on very darkly and diffusely. The nucleus is always eccentric, but this is its normal position in the retinal ganglion cells: it frequently projects on the surface, and sometimes a crescentic shrunken nucleus seems to form a sort of cap outside the contour of a balloon-shaped cell. The nucleolus is preserved up to an advanced stage of degeneration. Cells without a nucleus are found, but the appearance is probably due to peripheral cutting. The occurrence of nuclei not surrounded by protoplasm is probably due to the breaking up of the cell; such nuclei are

not always easily distinguished from those of the neuroglia, which are perhaps increased in number, but whereas the neuroglial nuclei are plump and show the normal reticulum, the others show the characteristic changes already described.

In the nasal half of the optic nerve a few broken-up and varicose nerve-sheaths are still stainable by the Weigert-Pal process. In hæmatoxylin-eosin specimens the nerve appears to be unduly cellular, perhaps from increase of neuroglia: the increase of cells is confined to the nervous substance, and does not affect the trabeculæ.

The above description sufficiently establishes the identity of the changes in the ganglion cells of the retina and of the central nervous system. This identity was first proved by Holden. The only notable point in which we differ from the excellent account of the changes in

FIG. 6.

× 600. Ganglion cells stained with hæmatoxylin and eosin. In the cell on the right the nucleus is much shrunken, in that on the left it projects beyond the cell body.

the central nervous system recently published in this periodical [6] is this, that whereas in that paper the nucleus is described as being usually "about normal" in size, in the present case it was almost invariably shrunken. We regret that the failure of Bielschowsky's method prevented us from studying the neuro-fibrils.

Our results are also essentially the same as those of other recent authors who have obtained the eyes sufficiently soon after death to be of much value.[1] From a study of these cases it may now be stated with certainty that folds and detachments at the macula, œdema of the retina,

[1] M. Cohen and G. S. Dixon. Eyes obtained two and a half hours *post-mortem*. F. H. Verhoeff: Eyes obtained fifteen minutes after death. In Mott's second case the eyes were excised immediately after death, but no pathological examination of them seems to have been recorded. According to Birch-Hirschfeld [7] the retinal ganglion cells begin to show *post-mortem* changes in two hours and their characteristic structure is lost in about seven hours.

holes in the fovea, and thickenings of the reticular and nuclear layers are artefacts, and due to imperfect fixation or *post-mortem* change. A hole in the fovea has been observed by one of us as a *post-mortem* change quite apart from amaurotic family idiocy.

The proof that a change in the protoplasm of the ganglion cells is capable of causing the ophthalmoscopic appearance of retinal opacity with a foveal cherry-red spot is of interest in connexion with the subject of obstruction of the central artery of the retina, and lends support to Elschnig's contention that the similar ophthalmoscopic changes in that condition are due not to œdema, but to a coagulation necrosis of the ganglion cell from the cutting off of their blood supply. The subject has been more fully discussed by us elsewhere (G. Coats [11], W. J. Hancock [12]).

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[7] Cohen, M., and Dixon, G. S. *Journ. Amer. Med. Assoc.*, 1907, vol. xlviii, p. 475.

[8] Mott, F. W. *Arch. of Neurology*, 1907, vol. iii., p. 218 (230).

[9] Verhoeff, F. H. *Arch. of Ophthal.*, 1909, vol. xxxviii, p. 107.

[10] Schuster, P. *Arch. f. Augenh.*, 1909, Bd. xlvi, S. 1.

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[11] Coats. *Roy. Ophth. Hosp. Reports*, 1905, vol. xvi, p. 293.

[12] Hancock. *Roy. Ophth. Hosp. Reports*, 1908, vol. xvii, p. 437.

[13] Mayou. *Trans. Ophth. Soc.*, 1904, vol. xxiv, p. 338.

Publications Recently Received.

[Notes on a book under this heading do not preclude a subsequent review.]

Ueber Geschwülste der hinteren Schädelgrube insbesondere des Kleinhirnbrückenwinkels. Von Dr. Folke Henschen. Mit 9 Tafeln. S. 283. Jena: Fischer, 1910.

The author has put together an account of twenty-eight cases of tumours in the posterior fossa of the skull. He divides them into a general group and tumours of the auditory nerve, which he calls tumours of the cerebellar angle, "par préférence." In the diagnosis, the most certain localizing signs are those due to affections of the cranial nerves, the trigeminal, the facial, or the auditory. Hearing should be investigated with unusual care, as the majority of the tumours in this region grow from the auditory nerve. Most of the cases discussed in the text are illustrated on the plates by drawings of the tumour *in situ*.

Eine eigenartige familiär-hereditäre Erkrankungsform (Aplasia axialis extracorticalis congenita). Von Privatdozent Dr. L. Merzbacher. Mit 40 Textfiguren. S. 138. Berlin: Springer, 1910.

In 1885 Pelizaeus described a curious family-disease of unknown cause. By a remarkable chance the brain of a member of this family came into the possession of the author, who was able to add ten cases to the four already described by Pelizaeus. The affected members of this family never walk, and show nystagmus and head-nodding from birth. The disease is transmitted by unaffected females, and twelve out of fourteen cases are males. Many become demented. The pathological change seems to be a destruction of the medulla of the nerve-fibres; axis cylinders are everywhere left naked in the central nervous system.

Konstitutionelle Verstimmung und Manischdepressives Irresein. Von Privatdozent Dr. Eduard Reiss. S. 282. Berlin: Springer, 1910.

The Swabians are known to be a quiet, somewhat brooding and melancholic race of the German people. The author, when assistant in the Tübingen Clinic, attempted to discover what effect this temperamental condition exerted on the functional psychoses, such as maniacal depressive insanity. He was able to observe 181 cases, and to see the patients after their cure. He came to the conclusion that temperamental depression in a people leads to a predominance of the melancholic forms amongst the insane. But during the course of these melancholias phases occur which bear little relation to temperament. The true circular insanities are quite uninfluenced by a constitutional tendency

to depression. This is a most interesting study, and deserves attention from all those interested in the developments we owe to Kraepelin and his school.

Text-book of Nervous Diseases for Physicians and Students. By Professor OPPENHEIM, of Berlin. Fifth enlarged and improved edition, with 432 illustrations in the text, and 8 plates. Authorized translation by ALEXANDER BRUCE, M.D. F.R.C.P.E., Physician to the Royal Infirmary, Edinburgh. Vols. 1 and 2. Pp. 1424. Edinburgh: Otto Schultze, 1911.

This is a faithful rendering into English of the last edition of Professor Oppenheim's text-book. It is well printed, and will be useful to all who cannot read this standard work in the original language.

Mentally Deficient Children, their Treatment and Training. By G. E. SHUTTLEWORTH, M.D., and W. A. POTTS, M.D. Third edition. Pp. 236. London: Lewis, 1910.

This well-known work has been brought up to date with the help of Dr. Potts. The facts of defective mental development in children are clearly given, and clinical types are shortly described. In many cases the descriptions are illustrated with excellent photographs. No better book could be placed in the hands of a medical man interested in the many questions which arise from mental deficiency in children.

The Brain and the Voice in Speech and Song. By F. W. MOTT, M.D. F.R.S. Pp. 112. London and New York: Harper, 1910.

This little book is clearly written in simple language, and technical terms are avoided. Not only the physics and physiology of voice production, but the nature of the mechanisms of speech are explained. As might be expected, the information is completely up to date, and the book will be useful to teachers and students of music who want to obtain a correct elementary knowledge of the voice.

Writers of "Original Articles and Clinical Cases" are supplied free of charge with 50 copies reprinted in the form in which the paper stands in the pages of "Brain." If reprints are required in pamphlet form, with wrapper, title-page, &c., and re-numbered pages, they must be ordered, at the expense of the writers, from Messrs. BALE, SONS & DANIELSSON, Ltd., 83-91, Great Titchfield Street, London, W.

Members of the Neurological Section of the Royal Society of Medicine can obtain the Index of "Brain" for the Volumes I. to XXIII. inclusive, that is, from its commencement to the end of 1900, from Messrs. MACMILLAN & CO., Ltd., St. Martin's Street, London, W.C., at the price of 6s. 6d., post free.

To those who are not members of the Neurological Section of the Royal Society of Medicine the price is 8s. 6d. net, and the volume may be obtained through any bookseller.

EDITOR.

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